ABSTRACTS OF WORLD MEDICINE

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Hygiene and Public Health

2206. **Age Distribution of Poliomyelitis in New York City in Relation to Previous Epidemics**
A. YANKAUER and H. P. GOLDBERG. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **38**, 1683–1687, Dec., 1948. 2 figs., 16 refs.

Recalling the assumption that if the virus of poliomyelitis becomes widespread during an epidemic a large number of passively immune infants might develop an active immunity from a modified form of the disease, the authors studied the age distribution of poliomyelitis in successive epidemics in New York City in 1931, 1935, and 1944. The criteria for acceptance in the cases studied are described, and the age distribution of cases in the 1944 epidemic is set out; the number of cases then arising in children who were under 1 year of age at the time of the 1931 and 1935 epidemics was found to be not lower than might be expected, and the authors conclude that no excess immunity was afforded to such individuals by their exposure to infection. *F. T. H. Wood*

2207. **Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses. III. Pulmonary Infiltrates and Mediastinal Adenopathy Observed Among Student Nurses at the Beginning of Training**
L. B. EDWARDS, I. LEWIS, and C. E. PALMER. *Public Health Reports* [*Publ. Hlth Rep., Wash.*] **63**, 1569–1600, Dec. 3, 1948. 19 figs., 4 refs.

Two sets of data, collected independently, are here brought together; they consist of radiological findings in student nurses starting training, and the results of antigen-sensitivity tests with tuberculin and histoplasmin. Some 23,000 nurses were studied. Many persons with pulmonary scarring and calcified nodules, which a few years ago would have been interpreted as residues of healed primary tuberculous infection, fail to react to tuberculin, but do react to the antigen histoplasmin. Possibly these healed lesions may be the end-products of an old infection with *Histoplasma capsulatum*, rather than of an old tuberculous infection. The way in which the two sets of data were collected is carefully described. The infiltrates detected radiologically were classified into 4 categories: (*a*) nodular; (*b*) poorly circumscribed; (*c*) fibrotic; and (*d*) "non-specific". The antigen sensitivities were also classified into 4 groups: (*a*) T−, H− (tuberculin negative, histoplasmin negative); (*b*) T−, H+; (*c*) T+, H−; and (*d*) H+, T+. A close relation was found between histoplasmin sensitivity and presence of nodular infiltrates. The circumscribed infiltrates were more closely associated with tuberculin sensitivity. The relations are well shown in a figure. The nurses studied came from 10 areas and differences were found in the prevalence of reactors in the areas, but the relation of the reactors to the antigen sensitivities was not materially modified. Among tuberculin reactors, the infiltrates were found in the upper portions of the chest; among the histoplasmin reactors, the infiltrates were scattered generally throughout the lung fields. Fibrotic infiltrates were composed essentially of strands alone. The frequency of calcification in nodular and fibrotic infiltrates was somewhat higher among histoplasmin reactors than among tuberculin reactors, but none of the poorly circumscribed infiltrates showed calcification unless associated with a positive tuberculin reaction. Few cases of progression were noted in the infiltrates at subsequent *x*-ray examinations, and such as were observed all occurred in individuals with infiltrates of the poorly circumscribed type associated with tuberculin sensitivity. The so-called "primary complex" of tuberculosis—that is, the combination of mediastinal adenopathy and associated parenchymal infiltrate—was observed only in individuals who reacted to histoplasmin alone or to both histoplasmin and tuberculin, and in no case in an individual reacting to tuberculin alone. The bearing of the findings of this study on the findings of mass radiography is clear.
E. L. Collis

2208. **Comparative Assays of Rodenticides on Wild Norway Rats. II. Acceptance**
S. H. DIEKE. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 593–597, Dec., 1948. 2 refs.

The author refers to his earlier published work on the toxicity of eight common rodenticides, in which he observed that high toxicity does not guarantee effectiveness under field conditions.

In the present article he describes a series of experiments extending over 18 months to test the same eight rodenticides as regards acceptability and effectiveness when offered to wild Norway rats in a standard bait under controlled laboratory conditions. For this purpose 565 wild Norway rats were used. Each rat was isolated for 14 days, fed on "purina fox chow" and water, and then transferred to an individual cage. At 4.30 p.m. each day the rats were given a weighed quantity of cornmeal. After 2 pre-baits on 2 successive nights, a weighed quantity of each of the 8 poisons was added to

the cornmeal. These included sodium fluoroacetate (" 1080 "), α-naphthylthiourea (ANTU), thallium sulphate, and zinc phosphide, which killed all rats at concentrations of 0·5% or lower. Arsenic trioxide required a concentration of 4% for a complete kill, whereas in the case of red squill there was a difference between the males and females, all concentrations failing to kill all males, whereas a 5% concentration was enough to kill all females. Barium carbonate, although it produced good kills in high concentrations up to 50%, failed to kill all animals in any concentration within the range tested. Finally, strychnine sulphate failed to kill more than a few rats in any concentration in the range. Another matter of interest is the fact that the rats consumed less bait as the concentration of poison was increased, except in the case of thallium sulphate, which would appear to be an ideal rodenticide except for its danger to human subjects. *H. C. Maurice Williams*

2209. **Pre-bottling Pasteurization of Beers and Sterile Filling**

W. J. WATKINS. *Journal of the Institute of Brewing* [*J. Inst. Brew.*] **54**, 295–299, Nov.–Dec., 1948. 6 figs.

Whereas much has been heard of the pasteurization of milk for babies, very little has been heard of the pasteurization of beer for fathers. Methods for sterilizing bottled beer were described in Germany before the war. The method depended on filtering the beers through a plate filler made up of sheets previously sterilized by steam or sulphur dioxide and impervious to bacteria. Attention is now directed to " flash " or bulk pasteurization before bottling in the " paraflow " type of plate heat exchanger. It is possible by adjusting pressures to control the carbon-dioxide content of bottling beers during heating and cooling in this machine.

G. M. Findlay

2210. **The Chronic Typhoid Carrier: I. The Natural Course of the Carrier State**

A. LITTMAN, J. A. VAICHULIS, A. C. IVY, R. KAPLAN, and W. H. BAER. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **38**, 1675–1679, Dec., 1948. 19 refs.

The authors point out that it has not been shown whether positive cultures obtained from typhoid carriers after a long remission do or do not represent re-infection, and report a study during 5½ years of 79 chronic carriers housed (68 from 1939 and 11 from 1941) at the Mentano State Hospital, Illinois; the carriers lived under one roof and were served from one kitchen, one-half of the helpers in which were typhoid carriers. At the start of the study, 49 had been carriers for 2 years, 11 for 3 months, and the remainder for intermediate periods, and an average of 30 cultures were made from each at average intervals of 22 months. At the end of the study in July, 1947, 19 patients (increased to 23 by March, 1948) were classified as " spontaneously cured ", refractory to re-infection, and had shown negative faeces and urine for intervals ranging from 33 to 66 months, or a duration of the carrier state of from 25 to 88 months. A striking sex difference was noted, in that none of the 26 male carriers was negative at the end of the period, whereas 23 of the 53 female carriers were negative.

Re-infection or recurrence (positive cultures after 3 negative monthly cultures) was found in 38 of the patients, who had 50 re-infections during the 5½ years, with no significant sex difference. The sex distribution of the cases contributing the carriers was equal, so that the preponderance of female over male carriers (53 to 26) is viewed as a true sex incidence. Cholecystograms taken before and after the 5½-year period revealed that no significant changes had occurred. [It may be pointed out that the passing of 5½ years reduced the proportion of females among the carriers from the 1939 epidemic to approximate equality with that of the males.]

F. T. H. Wood

2211. **Air Infection with Dust Liberated from Clothing**

J. P. DUGUID and A. T. WALLACE. *Lancet* [*Lancet*] **2**, 845–849, Nov. 27, 1948. 3 figs., 39 refs.

In an investigation in the Bacteriology Department, University of Edinburgh, very large numbers of bacteria attached to dust particles were found to be liberated from clothing, and the numbers varied greatly in proportion to the amount of movement of the wearer. A cotton surgical gown worn over ordinary clothing did not materially reduce the number of bacteria liberated into the air, but the numbers were greatly reduced by wearing a special dust-proof dress. Most of the bacteria found were harmless, but *Staphylococcus aureus* was isolated from the dust liberated from clothing worn by carriers of this organism. More staphylococci were liberated from the clothing of a carrier than by the act of sneezing.

Scott Thomson

2212. **The Recent Trend of Diphtheria in England and Wales**

W. J. MARTIN. *Monthly Bulletin of the Ministry of Health, etc.* [*Mon. Bull. Min. Hlth*] **7**, 232–236, Nov., 1948.

Before the introduction of widespread immunization, mortality rates from diphtheria in England and Wales fell from 888 per 1,000,000 children under 15 in 1901 to 301 in 1930. In 1940 the Government offered a prophylactic free to all local authorities. Since then the mortality has decreased more rapidly than the incidence: in 1946 deaths were 15% and notifications 30% of the pre-war levels. As a cause of death at ages 1–5 diphtheria was the third highest in 1937–8 and sixth in 1945; at ages 5–10 it was first in 1937–8 and third in 1945. The decline in attack rate has not been uniform throughout the country; London has had the most rapid fall, and the northern, south-western, and west midland counties and Wales the least. Urban districts show a slightly greater decline than rural. There has been a change in the age distribution of notifications, and in 1947 the pre-school child and adult were relatively more often attacked than in 1944, whereas the attack rate for age group 10–15 was in 1947 one-fifth of that in 1944. This is in direct contrast with the experience of preceding decades. *A. Michael Critchley*

2213. **Cholera Immunization**
E. SINGER, S. H. WEI, and S. H. HOA. *Journal of Immunology* [*J. Immunol.*] **60**, 181–187, Oct., 1948. 1 ref.

Vaccines of *Vibrio cholerae* were prepared in a number of different ways and injected into human beings subcutaneously and intradermally. The serological response was examined by agglutination reactions and by the neutralization of filtrates of *V. cholerae* which produce shedding of the epithelium of isolated guinea-pig intestine. The antibody response did not appear to depend on the method of manufacture of the vaccines. Following the third intradermal injection of vaccine a sterile abscess often appeared. *Scott Thomson*

2214. **Studies in Dysentery Vaccination. IV. Primary Vaccination of Children with Monovalent Vaccines of Shigella**
M. L. COOPER, J. TEPPER, and H. M. KELLER. *Journal of Immunology* [*J. Immunol.*] **60**, 189–203, Oct., 1948. 19 refs.

Vaccines prepared from several different types of *Shigella flexneri* were injected intravenously, subcutaneously, or intradermally into adolescents. Samples of serum from the inoculated persons were collected at intervals thereafter and examined *in vitro* by agglutination tests and *in vivo* by mouse-protection tests. Mouse-protecting antibodies were demonstrated in considerable amount against the type used in the vaccine, but there were appreciable cross-reactions with other types. The inoculated persons were not at any time exposed to dysentery. [The article contains no correlation between the tests on samples of serum and the real resistance in the inoculated.] The authors are of the opinion that "agglutination tests . . . were less satisfactory than the mouse-protection test for differentiating degrees of immune response". *Scott Thomson*

2215. **The Uses of D.D.T. in Bug Extermination in Slum Properties**
W. C. GUNN. *Medical Officer* [*Med. Offr*] **8**, 251–252, Dec. 4, 1948.

Some 204 bug-infested houses or apartments [the author sometimes refers to houses and sometimes to apartments] were treated with the following insecticidal solutions—the numbers in brackets referring to the number of houses treated—5% DDT in kerosene (36); 10% DDT in kerosene (3); 5% DDT emulsion (124); 10% DDT–water emulsion (4); 0·35% "gammexane" solution (22); 5% DDT in kerosene ("H.M.5") (10); gammexane smoke generator (1); "fumite" (DDT smoke generator) (4). Beyond the somewhat vague statement that "the application of the insecticide has been on a generous scale and the average has been nearly one gallon (4·5 litres) per apartment", no reference is made to the final concentration of the insecticide in the treated rooms. The houses which had been sprayed were visited on 3 or 4 occasions during the ensuing 4 months, and the number found free from bed-bugs, or still infested, was recorded. Of the 4 houses treated with fumite, bed-bugs were still present in 2 houses 3 to 4 months later. Complete eradication of the bed-bugs appears to have followed the use of all other insecticides. [Although it is clear from this paper that the speed of elimination of the bugs was not the same in every instance, the data given are not sufficient to draw any conclusions regarding the relative efficiency of gammexane and DDT. The author states that "a 5% water emulsion of DDT" gives as good results as a 5% solution in kerosene. No reference is made to the findings of previous authors, but this last claim is not in accordance with the earlier observations.]
R. M. Gordon

INDUSTRIAL MEDICINE

2216. **Technical Aspects of the Los Angeles Smog Problem**
H. F. JOHNSTONE. *Journal of Industrial Hygiene and Toxicology* [*J. industr. Hyg.*] **30**, 358–369, Nov., 1948. 1 fig., 34 refs.

Much publicity has been given to the increasing atmospheric pollution in the Los Angeles area of the U.S.A. Occasionally its concentration is so marked as to cause severe irritation of the eyes and throat. The pollution is to a large extent due to the topographical and meteorological features of the Los Angeles basin. The prevailing winds in the day-time carry the dust and fumes from the industrial district into the residential sections. This is due to the existence of an inversion layer with a negative temperature gradient between the 1,000- and 3,000-foot (300 and 900 m.) elevations. It reduces the atmospheric turbulence and prevents the normal rise and dilution characteristic of smoke clouds. Secondly, the high and extensive mountain ranges to the north and east act as barriers to intercept air movement. At night the winds from the mountains carry the pollution back over the city and industrial area.

Exact information on the nature of the "smog" is lacking, but certain aspects of the problem are related to the general properties of aerosols. When the particles of an aerosol are large it is common to speak of the system as a fog, mist, or cloud. If the suspended material is the result of combustion or of destructive distillation it is commonly called smoke. Fume, which may be either solid or liquid, is produced by volatilization, while dust is derived from natural and mechanical processes of disintegration. The blue haze which contributes to low visibility in the Los Angeles area is usually associated with aerosols of very small particle size, 0·3 to 0·5 μ in diameter. Solid particles serve as nuclei of hygroscopic particles and droplets in a natural fog, and range from 5 to 50 μ in diameter. During the war it was shown by tests on screening that the optimum particle size for greatest obscuration depends on the refractive index of the dispersed material and the wave-length of the incident light. For instance, for oil smoke the maximum screening efficiency is obtained when the droplets have a diameter of 0·6 μ, while for sulphur smoke, which has a

higher index of refraction, the maximum obscuration is obtained when the particle diameter is 0·3 μ.

Various methods are suggested for the removal of dust, fumes, and sulphur pollution products from the atmosphere, though not with any special reference to Los Angeles. They include cyclones, " gas scrubbers and washers, and electrostatic precipitators ".

H. M. Vernon

2217. **Systematic Study of 100 Workers Using Pneumatic Tools.** (Examen systématique de cent ouvriers se servant des outils pneumatiques dans les travaux publics) B. DESPLAS, V. RAYMOND, and P. BERNARD. *Archives des Maladies Professionnelles* [*Arch. Mal. prof.*] **9**, 388–405, 1948. 13 figs., 5 refs.

Investigations were carried out on 101 workmen who handled pneumatic tools. The tools varied in weight from 12 to 45 kg. and had striking frequencies between 1,500 and 3,000 per minute. Most of them were used vertically. The ages of the men ranged from 23 to 66 years with an average of 43 years. Some had worked for only a few weeks, others for 40 years; most had worked for 10 or more years. As a rule 2 men worked with each tool during an 8-hour day, sharing the work between them. Most of the men were well developed; about a dozen made spontaneous complaint of various pains and many others did so when questioned. Seven men suffered from finger pallor, and stiff or crepitant joints were found in 3 others. Of the 101 workers 16 were examined in detail. Radiographs showed various patches of decalcification in bone, usually in the carpus. Some men had exostoses or intra-articular and more commonly extra-articular foreign bodies. Some epiphyses were malformed.

The authors consider vacuolation of bone to be the typical lesion and it was found in 40% of the cases examined. The os magnum was the most frequently affected, then the semilunar and the scaphoid. Many of the changes seen in the os magnum are thought to have followed old fractures which had not been diagnosed. Attention is drawn to Böhler's view that Kienböck's disease of the semilunar is occupational and commonly occurs in those who make sudden and repeated dorsiflexion of the wrist. Ossifications of tendons were sometimes noted, generally round the elbow. No reference is made to vascular disease and the authors conclude that most of the workers observed may safely continue their usual tasks.

G. C. Pether

2218. **Job Performance of Physically Impaired Persons in Industry**
J. S. FELTON. *Occupational Medicine* [*Occup. Med.*] **5**, 466–495, May, 1948. 3 figs., 4 refs.

The Oak Ridge National Laboratory employed 452 (11·1%) people with physical limitations. The performance of 300 of these is compared with that of 300 normal controls. The classification of applicants for work was as follows: (1) any work; (2) any work, in spite of minor defects; (3) certain jobs, with specified restrictions of activity; and (4) no employment. Those with limitations were " placed " after reference to analyses of job requirements; 59% fell into category 2 and 13% into category 3. Their performance was measured on the opinions of their supervisors, a separate rating being given for quality of work, quantity of work, knowledge of the job, adaptability, judgment, dependability, attitude, attendance, punctuality, and ability. In the hope of getting greater objectivity, supervisors were given a standard form to complete in which reasons for each rating were set out.

Each group comprised workers in many trades. The groups were fairly comparable as regards age, sex, race, marital state, and length of employment. The disabled men had all types of abnormality: 32·6% had hernia. An assessment of emotional adjustment, based on the answers given to significant items in a questionary consisting of 200 queries (Cornell index), was made for comparison. Accident rates also were compared. The average scores of the two groups did not differ as regards punctuality, attendance, or attitude, but the quantity of work done appeared to be greater in the " impaired " group, despite the variety of jobs, while scores for ability and quality of work were rather better in the unimpaired. The impaired workers had a slightly higher average Cornell index (that is, they had a greater tendency to neurosis). The physically normal group had a significantly higher accident rate, but the number of injuries per worker was the same in both groups. The total scores suggest no significant difference between the job performance of the normal and impaired groups, or between the larger subgroups of the impaired, for example, those with cardiovascular disease, hernia, or tuberculosis. There was a low correlation between the Cornell index scores and the supervisors' ratings; the former gives little indication whether or not a man is adjusted satisfactorily to his job. The author concludes that these performances reveal the fallacy of applying rigid physical standards in industry, and that disabled persons are valuable, productive, and safe employees. [Physical impairment and disability are confused here. The former was determined at pre-employment examination, and all varieties seem to have been included, regardless of whether a worker was handicapped in the job he was given. Measurements of job performance take no account of individual workers' problems. Many workers left before their performance could be studied.]

J. N. Agate

2219. **Employment of Persons with Pulmonary Tuberculous Lesions**
M. W. JOCZ, J. J. PRENDERGAST, and C. C. BIRKELO. *Occupational Medicine* [*Occup. Med.*] **5**, 496–505, May, 1948.

Between 1942 and 1946 a group of physically " substandard " workers were studied by the medical organization of an engineering firm. Only those capable of full-time work were accepted, and no special recommendations as to job were made, except to forbid exposure to silica. The chests of all new applicants for jobs were radiographed as a routine, but old employees were radiographed only if there were definite indications.

At 241,000 examinations made in one area active pulmonary lesions were found in 661 people, and these were considered unemployable; 1,757 others with inactive lesions were accepted for employment or re-employment. Most of those with active lesions were fresh applicants and were not aware of their disease. The greatest number of tuberculous applicants was seen in 1943, because most healthy men had entered the armed forces; some men had obviously left sanatoria against advice in order to do war work.

Of all those with tuberculosis, 8·9% had had sanatorium treatment; nevertheless, one-fourth of them had active lesions and were unemployable. The authors were impressed by the staying power of 21 workers with thoracoplasties and inactive lesions. During the period of study 173 people out of the 241,000 developed active lesions; 39 had known lesions which were considered inactive at the outset; in 51 the films had been normal; 83 had developed lesions but had had no initial radiograph. The 39 with known lesions worked for an average of 21·8 months before activity was discovered. A rate of 1·25% for activation of inactive lesions is suggested. The 51 originally considered normal worked for an average of 28·2 months before the disease developed. In the 5-year period 47 individuals with active lesions were able to return to work after adequate therapy lasting for an average of 15 months. There was no unusual concentration of active disease in any department. The authors conclude that the employment of persons with certain types of inactive pulmonary disease is practicable, that such employment in a highly mechanized industry does not harm these persons or their fellow-workers, and that the work record of tuberculous employees is as good as that of other substandard employees. [No evidence is given to support the last conclusion.] *J. N. Agate*

2220. **Aerosols. IV. Effect of Saline Aerosols on Dust in Atmosphere; Reduction of Dust Deposition in Lungs by Saline Aerosols**

L. Dautrebande, B. Highman, W. C. Alford, F. L. Weaver, and E. C. Thompson. *Occupational Medicine* [*Occup. Med.*] **5**, 506–521, May, 1948. 9 figs., 11 refs.

Solutions of salts (as aerosols) agglutinate dusts more readily than do water aerosols. The effect of 5 to 10% sodium chloride aerosols on fine willemite dust suspensions was investigated. This dust fluoresces in ultraviolet light. A dust cloud with particles of 0·49 μ apparent mean size at 1,125 diameters magnification was generated. Samples were collected by sedimentation in a chamber. The true mean size was probably much smaller. Dust of such small particle size cannot be suppressed by water sprays. The first experiment showed that it can penetrate a continuous liquid barrier, as when the air containing it is passed through water in a flask. Secondly, dusty air diluted with saline aerosol was passed through a flask of water before sedimentation; the experiment was repeated with clean air as the diluent in place of the aerosol. In the former case most of the particles appeared as aggregates and the discrete ones were coated with liquid. Thirdly, a dust current was divided and passed continuously into sedimentation chambers, after being diluted in one case with clean air and the other with saline aerosol, and washed. Industrial conditions were thus reproduced more closely. In the chamber with the untreated dust the mean diameter of the discrete particles was 0·61 μ and of the aggregates 1·7 μ, but in the chamber with the aerosol diameters were respectively 2·5 and 7·2 μ, with a wider scatter in the latter case. Thus the aerosol can effectively coat and agglutinate particles of this size.

Groups of rabbits were exposed for 5 hours in a chamber containing 24 to 132 mg. per cubic metre of willemite mixed with normal air, and compared with similar groups of rabbits exposed to dusty air mixed with saline aerosol. Sections of the lungs were stained with azure eosinate, and others were micro-incinerated for examination under ultraviolet light. Estimates were made of the numbers of particles per 10 fields. The aerosol greatly lessened the quantity of dust deposited, and during the experiment the animals remained more active than those exposed without the aerosol. The experiment was repeated with washed dust to simulate conditions during wet rock drilling, and the same results were obtained. Passage through a layer of water did not lessen the effectiveness of the aerosol. Similar results were obtained after longer exposures to treated and untreated dusts; when an interval was allowed to elapse between the exposure and the killing of the animal, no dust was seen in the bronchi and very little in the parenchyma. This suggests that saline aerosol treatment shortens the period of dust retention in the lungs. The respiratory rates of animals exposed to treated dusts were lower than in those exposed to untreated dusts.

J. N. Agate

2221. **A Tropical Occupational Disease due to Derris, with Investigations of the Effect of Derris on Goldfish.** (Eine tropische Berufskrankheit durch Derris mit Untersuchungen über die Wirkung von Derris auf Goldfische)

R. D. G. P. Simons. *Acta Dermato-Venereologica* [*Acta derm.-venereol., Stockh.*] **28**, 601–618, 1948. 10 refs.

The bark of the derris root is a well-known fish poison and contains rotenone, degueline, tephrosine, and toxicarol. Lately it has also been used as an insecticide. In the author's experiments with goldfish, derris powder was found to exert a stronger lethal action than did rotenone. From the literature some fatal cases of derris poisoning are described. The symptomatology of less severe poisoning is illustrated by a number of cases occurring among the workers in a derris factory in Java. The symptoms include dermatitis and irritation of the mucous membranes—rhinitis, conjunctivitis, pharyngitis, laryngitis, and balanoposthitis. Apart from these, pruritus ani, loss of taste and appetite, nausea and vomiting, and abdominal pain may occur. The author cautions against the use of derris in medical preparations —such as anthelmintics, derris soaps and ointments— and, apart from their possible toxic effects, believes that their medical value is exceedingly doubtful.

G. W. Csonka

Genetics

2222. **The Viability of Individuals Heterozygous for Recessive Lethals**
C. STERN and E. NOVITSKI. *Science* [*Science*] **108**, 538–539, Nov. 12, 1948.

By definition a recessive lethal gene is a gene which kills its carrier in the homozygous state while the heterozygote is viable. In most work on population genetics, the assumption is tacitly made that the heterozygote is as viable as a homozygous normal individual. This question has now been put to the test by the authors, who investigated, in the fruit-fly *Drosophila melanogaster*, 7 spontaneous sex-linked lethal genes and 27 sex-linked lethal genes obtained in irradiation experiments; of the latter, many were probably not due to the experimental treatment. The result was that in the majority of cases the heterozygote was less viable than a homozygous normal individual; hence most of these genes are not completely recessive. The viability of the heterozygotes was reduced down to 90% of the normal or less. This has a practical consequence. In a population, a rare gene is mainly represented by heterozygotes which may be hundreds of times more abundant than the lethal homozygotes. Now a reduction of the viability of the heterozygote by, say, 5% will, in the aggregate, result in a greater loss of fitness to the population than the complete elimination of the occasional homozygote.
H. Grüneberg

2223. **A Sex-limiting Modifying Gene in Diaphysial Aclasis (Multiple Exostoses)**
H. HARRIS. *Annals of Eugenics* [*Ann. Eugen., Camb.*] **14**, 165–170, Nov., 1948. 4 refs.

Diaphysial aclasis is far more common among men than among women. There is no clear evidence that a male can transmit the condition without himself being affected, but there is definite evidence that the disease can be transmitted by females themselves unaffected. Finally, affected males tend to have a higher incidence of affected sons amongst their offspring than do affected females, whilst affected male grandparents are liable to have a higher proportion of affected males among their grandchildren than do affected female grandparents. It would seem therefore that, whereas there is more or less full manifestation of the gene in the male there is only partial manifestation in the female. The high sex ratio observed amongst affected individuals in the population would seem to be due to the fact that the gene manifests itself in practically all males who carry it but only in a proportion of females.

The author began this present study with a working hypothesis that the failure to develop this condition by a female carrying the appropriate gene was due to the presence of modifying genes. If this was so then such modifying genes would be present in all unaffected females known to be transmitters but only occasionally, if at all, in affected females. It would then be expected that there would be evidence of the activity of such modifying genes amongst the offspring of matings between unaffected males and unaffected females known to be transmitters, and relatively little evidence of their presence in offspring of unaffected males and affected females. When all the available data were collected and arranged it was found that there was a significant deficiency of affected females in the offspring of the unaffected female transmitters.

If the gene for this condition finds full manifestation in the male and only partial manifestation in the female, and if this difference is due to the occurrence of genes which by their presence in a female tend to suppress the development of the condition, then it becomes possible to draw certain other conclusions from the results of the following matings: (1) affected father and unaffected mother; (2) unaffected father and affected mother; (3) unaffected father and unaffected mother known to be a transmitter; (4) unaffected father and unaffected mother with no definite information as to who is the transmitter. If the hypothesis is warrantable then in the vast majority of instances of class 4 there will be an unaffected father and an unaffected but transmitting mother, and the sex ratio of the affected offspring of all parents of class 1 should be the same as the sex ratio of the sum of the affected offspring of parents of classes 2, 3, and 4. Finally, the affected offspring of classes 3 and 4 should show a far higher sex ratio than the affected offspring of class 2. The results obtained in this study were all in the direction expected from the hypothesis. It seems possible that the gene concerned is a single autosomal modifying gene.
F. A. E. Crew

2224. **Two Examples of Sera Containing the Anti-d Agglutinin Predicted by Fisher and Race**
J. M. HILL and S. HABERMAN. *Nature* [*Nature, Lond.*] **161**, 688–689, May 1, 1948. 9 refs.

The authors report the finding of two examples of the Rh agglutinin anti-d. [Though this antibody has been looked for since 1944 its discovery has only once been reported (Diamond, Rh and Hematology Congress, Dallas, 1946).] The first of the two examples was in a woman of the genotype CDe/CDe; the anti-d agglutinin was active in saline and anti-c was also present. The presence of anti-d was shown by the ability of the serum to agglutinate CDe/Cde cells. The second serum also contained anti-c as well as anti-d, but the presence of the anti-d agglutinin was easily detected, for it was in the saline-agglutinating form while the anti-c was in the incomplete form. The authors also confirmed the presence of the two agglutinins in each serum by their quantitative haemolysis test. Tests on 155 random samples of erythrocytes with the anti-d serum resulted in the agglutination of 65·16%; the figure calculated by Fisher for the positive reactions given by this antibody, when it should be found, was 64·43.
R. R. Race

Anatomy and Cytology

2225. **Nuclear Structure Versus Nuclear Pattern**
O. P. JONES. *Blood* [*Blood*] **3**, 967–986, Sept., 1948. 5 figs., 40 refs.

Lymphocytic cells derived from the livers of rat embryos and the human foetus, from the blood of rat embryos, and from the lymph nodes of adult rats have been studied by microscopy and by bright-contrast and dark-contrast phase microscopy. Cells were mounted unstained in a drop of 10% formalin and ringed for phase microscopy. Other preparations were stained by the May–Grünwald–Giemsa combination, neutral red, dahlia violet, Janus green, aniline acid fuchsin, sudan black, and the Carr–Price vitamin-A reagent. Freshly dried smears preserved cytoplasmic detail with a great degree of accuracy. The lymphocytes derived from the blood show cytoplasmic sudanophobic vacuoles (appearing as light vacuoles by dark-contrast phase microscopy and staining with neutral red) in the juxtanuclear position which are considered to represent a Golgi apparatus. Optical sections through different layers of the cells derived from foetal livers show by phase microscopy the distribution of cytoplasmic organoids (mainly mitochondria) above and below the nucleus. The negative images of these organoids are seen in the nuclear pattern and have been previously described as parachromatin. These negative areas straddle the nuclear membrane. Nuclear structure as seen in histological or optical sections consists essentially of nuclear membrane, basi- and oxy-chromatin reticulum, linin, nucleoli, and karyoplasm. In contrast, nuclear pattern as seen in dry smear preparations represents the sum total of the foregoing nuclear structure and negative images of the cytoplasmic organoids. These two descriptive entities require differentiation.

J. Maclean Smith

2226. **The Intraneural Topography of the Sciatic Nerve and its Popliteal Divisions in Man**
S. SUNDERLAND and L. J. RAY. *Brain* [*Brain*] **71**, 242–273, 1948. 19 refs.

The morphology of the sciatic nerve and its popliteal divisions was studied by dissection and serial section in material from 40 adult dissecting-room subjects. The investigation was carried out with reference to: (1) the behaviour of constituent funiculi and the fibre composition; (2) the distance above the site of branching for which funiculi retained their identity and position before participating in plexus formations; and (3) the nature and extent of the redistribution of the various branch fibres resulting from migration, division, and anastomosis. It was found that the larger the course of a branch within a nerve the greater were the mixing and diffusion of its fibres at proximal levels. The pattern of the main nerve trunk was constantly changing as a result of repeated division, anastomosis, and migration of funiculi. The largest section of nerve showing a constant pattern was 6 mm., though individual bundles and bundle groups ran longer courses. In the lateral popliteal nerve the number of bundles in the lower third of the thigh was often only one or two.

[This paper is so detailed and factual as to render a full summary impossible. Those interested should consult the original.] *R. Barer*

2227. **Observations on the Foramen of Magendie in a Series of Human Brains**
M. L. BARR. *Brain* [*Brain*] **71**, 281–289, 1948. 7 figs., 11 refs.

The region of the roof of the fourth ventricle was examined in 118 adult human brains removed at necropsy and fixed in formalin; special care was taken to avoid tearing the roof. The morphology of the foramen of Magendie showed some variation, but several main groups were distinguished. In 56% of the brains the foramen appeared as a wide-open gap in the roof. The margins were formed by the posterior border of the pia-ependymal roof and the lateral margins of the floor of the fourth ventricle. The pia-ependymal roof was reflected upwards towards the inferior vermis between the paramedian lobules of the cerebellum. The commonest variations were due to differences in the mode of attachment of the roof to the cerebellum. In 23% the pia-ependyma did not extend along the inferior surface of the cerebellum for any distance. The outlines of the foramen in such cases were well defined, as depicted in most textbooks. In 10% the choroid plexus showed a considerable posterior prolongation beyond the limits of the paramedian lobules. The boundary between the fourth ventricle and the cisterna magna was indistinct, and part of the choroid plexus appeared to secrete cerebrospinal fluid directly into the cisterna magna. In the remaining brains the roof of the fourth ventricle was more intact than in the preceding cases. In 7% the roof was complete in the midline for a variable distance anterior to the obex. In 3% the foramen was exceedingly small, and in one specimen no midline aperture was present. The foramina of Luschka were present in all specimens and could be identified by a tuft of choroid plexus projecting into them from the lateral recesses of the fourth ventricle.

The possible implications of these findings in encephalography are discussed. In about 6% of cases the foramen of Magendie is so small as to present a partial obstruction between the subarachnoid space and the fourth ventricle. On morphological grounds it would appear unlikely that the foramina of Luschka would be of much importance as a means of entry of gas into the ventricles. *R. Barer*

Physiology and Biochemistry

2228. **The Inhibitory Effect of the Oxygen Pressure in Blood on Respiration through the Intermediacy of Chemoreceptors.** [In English]
P. A. A. WETERINGS. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 232–258, 1948. 5 figs., bibliography.

The author discusses the influence of pulmonary ventilation on the oxygen and carbon-dioxide content of alveolar air and arterial blood, and reviews previous experimental work on chemoreceptors. Clinical observations on patients under continuous oxygen therapy are recorded. The view that the " normal desaturation " of arterial blood acts as a stimulus to respiration, which is increased in intensity by further desaturation, is contested. The hypothesis is advanced that the effects of oxygen lack are due to a specific inhibitory effect of oxygen on respiration. Experiments are recorded which indicate that the percentage of alveolar carbon dioxide may rise to 9% during elevation of alveolar oxygen pressure without increase in ventilation. The apnoea of hyperventilation is thus attributed to a relative predominance of oxygen pressure during the lowering of carbon-dioxide pressure. Oxygen and carbon-dioxide pressures constantly influence respiration, and alterations in the alveolar pressure of either gas will alter pulmonary ventilation through the mediation of the chemoreceptors. *E. F. McCarthy*

2229. **Definition, Estimation, and Physiological and Pathological Significance of Phenolsteroids.** (Définition, dosage et intérêt physiopathologique des phénolstéroïdes)
M.-F. JAYLE, M. LACOMME, O. CRÉPY, and O. JUDAS. *Annales d'Endocrinologie* [*Ann. Endocrinol., Paris*] **9**, 316–327, 1948. 1 fig., 4 refs.

The term " phenolsteroids " includes oestrone, oestradiol, oestriol, and other substances with little or no biological activity which are possibly precursors or metabolic products of the oestrogens. They were estimated by the addition of 4·64% β-naphthol in sulphuric acid (Kober's reagent) to purified ether extracts of urine hydrolysed by acid after collection on 3 successive nights without preservative; the light absorption was estimated at once on the photoelectric colorimeter, the colour developed being due to phenolsteroids and urinary pigments, and again 24 hours later when it was due to urinary pigments alone; subtraction of the second reading from the first gave the index due to the phenolsteroids. The concentration of the latter was calculated by reference to a calibration curve prepared from a solution of purified oestrone, results being expressed as the excretion during 24 hours. The technique of extraction, purification, and estimation of phenolsteroids is given in detail. It is accurate for concentrations of 300 μg. or more per day; with amounts below 300 μg. the estimation is only qualitative.

Results of estimations throughout 8 normal menstrual cycles showed an initial peak varying from 130 to 300 μg. per day at about the 4th day, a second rise at about the 13th to 14th day of 225 to 420 μg., a luteal plateau from about the 19th to the 25th day between 200 and 285 μg., and a premenstrual fall to about 130 μg. If pregnancy supervened, the luteal plateau was prolonged beyond the presumed date of the next period without any marked subsequent rise, excretion at the end of the first month averaging 325 μg.; there was a gradual increase until 2½ months, the amount being approximately doubled between 2½ and 3 months, and from 3 to 6 months the excretion increased on an average by 750 μg. every fortnight. From 6 to 7 months the excretion is maintained at about 6,000 μg., and from 7½ to 8½ months there is a very sharp rise to a peak of 11,525 μg., which is maintained until term.

Men excreted 200 to 250 μg. of phenolsteroids in 24 hours. In newborn infants there was a progressive fall from 229 μg. per litre of urine on the first day of life to the 5th day when no phenolsteroids could be demonstrated. After the menopause or surgical castration only traces of phenolsteroids were usually found, though exceptions are described. Amenorrhoea can be classified on the basis of phenolsteroid excretion.
Walter H. H. Merivale

2230. **Renal Plasma Flow during Moderate Exercise of Several Hours' Duration in Normal Male Subjects**
C. B. CHAPMAN, A. HENSCHEL, and A. FORSGREN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 170–171, Oct., 1948. 1 fig., 2 refs.

Experiments were carried out on normal males to demonstrate the effect on renal blood flow of 3 hours' moderate exercise. The authors estimated the renal plasma flow by using *para*-aminohippurate for renal clearance tests. [In this method the substance chosen is injected so as to cause a certain concentration in the plasma. At this concentration it can be eliminated from the plasma in one passage through the active renal tissue. From determinations of the concentration of the substance in the plasma and in timed urine samples the amount of plasma—and therefore, by calculation, of blood—passing through the kidney in a given time can be estimated.] A moderate water diuresis was instituted to enable samples of urine to be collected for analysis at frequent and known intervals.

A gradual decrease was seen during the first hour of exercise, at the end of which time the renal flow had fallen to about 65% of normal. This level was sustained without significant further change for the next 2 hours of mild exercise. The renal blood flow returned almost to normal in 40 minutes to 1 hour after ending the work. This recovery was rapid, considering the length

of the exercise. The adjustment of the renal blood flow in response to moderate exercise is therefore clearly defined, but is not as rapid as other circulatory changes. Thus, in mild or moderate work the pulse rate and oxygen consumption reach their maximum 10 to 15 minutes after starting, compared with 1 hour in the case of the renal blood flow. *R. P. Foggie*

2231. **Effect of Muscular Exercise on Dark Adaptation**
J. P. WENDLAND. *American Journal of Ophthalmology* [*Amer. J. Ophthal.*] **31**, 1429–1436, Nov., 1948. 1 fig., 15 refs.

Moderate exercise has little effect on the rate of dark adaptation, but heavy exercise causes some elevation of the thresholds of the total dark-adaptation curve. There is at first a lowering of the threshold, of short duration, followed by a large rise in the threshold which lasts longer. The practical aspect is that heavy exercise causes a definite decrease in the ability to see at night.
A. G. Cross

CIRCULATORY SYSTEM

2232. **Rate of Flow of Venous Blood in the Legs Measured with Radioactive Sodium**
H. P. WRIGHT, S. B. OSBORN, and D. G. EDMONDS. *Lancet* [*Lancet*] **2**, 767–769, Nov. 13, 1948. 3 figs., 12 refs.

As a preliminary to later investigations of venous blood flow in pathological conditions associated with venous thrombosis, a study was made in normal persons of the rate of venous blood flow up the legs, by injecting $Na^{24}Cl$ into a foot vein and timing the arrival of the radioactive material in the groin. In 121 subjects after warming until the foot temperature was 33° C. the mean flow time was $18 \pm 0{\cdot}9$ seconds (extreme values, 4 and 50 seconds). In 10 of the subjects in whom the foot and leg were also warmed from 45° to 48° C. determinations did not differ significantly from those obtained at 33° C.
R. A. Gregory

2233. **Studies on the Neurochemical Mechanism Regulating Arterial Blood Pressure.** (Ulteriores estudios sobre el mecanismo neuroquímico de regulación de la presión arterial)
C. JIMÉNEZ DÍAZ, P. DE LA BARREDA, A. F. DE MOLINA, and B. MACHADO. *Revista Clínica Española* [*Rev. clín. esp.*] **31**, 24–29, Oct. 15, 1948. 5 figs., 13 refs.

The authors discuss the mechanism by which a fall in blood pressure is obtained when the carotid sinus of the dog or the depressor nerve of the rabbit is electrically stimulated; 16 dogs and 6 rabbits were used. Hypotension produced by such stimulation remains unaffected after bilateral nephrectomy, adrenalectomy, and vagotomy. The hypotensive effect can be transmitted to another animal by means of vascular anastomosis and perfusion from the stimulated animal. At one stage of the experiments the femoral and the carotid circulations of the dog were made independent of each other by means of appropriate ligation. To demonstrate that this independence was complete the authors injected adrenaline and observed the effect on both circulations; all the nervous connexions remained unaltered. In these conditions electric stimulation of the carotid sinus produced hypotension in the superior-carotid-irrigated area, while the blood pressure remained unaffected in the femoral territory. The authors state: "We must admit the formation in the superior part of the dog of a substance which, circulating, produces a general hypotension". The histamine level in the blood before, during, and after the stimulation did not vary; therefore this hypotensive substance could not be histamine; neither could it be acetylcholine, as further [and not very accurate] investigation seemed to show. The authors are led to believe that this hypotensive substance is formed in the liver, because in a previous series of investigations they found that "when hypertension is provoked by stimulating the proximal end of a divided vagus nerve, this hypertension lasts much longer when the liver is excluded from the circulation". It is assumed that the exclusion of the liver prevents the "hypotensin" from reaching the circulation.
A. Lilker

2234. **Effect of Climate on the Blood Pressure in Acclimatized Subjects**
L. P. R. FOURMAN. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. R. Soc. trop. Med. Hyg.*] **42**, 299–301, Nov., 1948. 3 refs.

In sailing from the Red Sea to the Mediterranean, there is a sudden fall in temperature and humidity. Observations were made on the effect of this change in climate on the blood pressure. Forty-five subjects of varying ages and 3 patients with hypertension were studied under resting conditions. There was no significant change in the blood pressure when the relative humidity diminished by about 20%.—[Author's summary.]

2235. **Heart Rate in Recovery from Severe Exercise**
H. HERXHEIMER. *Journal of Applied Physiology* [*J. appl. Physiol.*] **1**, 279–284, Oct., 1948. 2 figs., 17 refs.

The delayed recovery of the resting pulse rate after severe exercise has been attributed to vasodilatation. This paper records an attempt to determine the extent of the vasodilatation and to ascertain whether it could be prevented by bandaging the limbs. The subjects were 4 trained boy cyclists. The initial pulse rate was counted after a 10-minute rest in the horizontal position. Subsequently the subject was exercised on a bicycle ergometer adjusted so that severe dyspnoea set in during the third minute and continued to the end of the fifth minute. The oxygen consumption was computed to be between 3,500 and 3,800 c.c. per minute during the dyspnoeic period; in two experiments the initial oxygen consumption was re-attained, with the subject seated, after 43 and 57 minutes. In half the experiments elastic bandages were applied immediately after the exercise, and the pulse rate was taken with the subject in the horizontal position

until a basal value was reached, when the bandages were removed and the pulse rate counted for a further 15 minutes. Limb volumes were also measured, a crude plethysmograph being used. In all but two experiments the pulse rate reached its basal value more quickly when the limbs were bandaged. The leg volume increased in all experiments after exercise to an average of 275 c.c. [These experiments do not permit the duration of the post-exercise vasodilatation to be determined.]

C. C. N. Vass

2236. **Blood Volume Determination in the Human with Red Cells Containing Radioactive Phosphorus (P^{32}) and with Pure Human Albumin**

F. J. KELLY, D. H. SIMONSEN, and R. ELMAN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 795–804, Nov., 1948. 1 fig., 43 refs.

A method is described by which erythrocytes containing radioactive phosphorus are used to measure blood volume in human subjects. Blood volume changes as measured by the effect of an intravenous injection of plasma and pure human albumin were also observed. In each determination of blood volume 50 microcuries of radioactive phosphorus (nuclear mass 32) was used. This amount corresponds to less than 0·01 r equivalents physical per day for 100 days, the accepted limit of tolerance for man being 0·1 r per day. The half-life of the radioactive phosphorus [that is, the time taken for the radioactivity to fall to half strength] is 14·3 days.

In principle the method consisted in mixing 1 to 2 ml. of a solution containing 50 microcuries of radioactive phosphorus with 15 ml. of heparinized venous blood from the subject. The mixing was done by inversion followed by mechanical agitation for 2 hours at 37° C. At the end of this period 10 ml. of the mixture was injected into the patient, and specimens were removed at various intervals from the opposite arm. Samples of both the injected blood and that obtained subsequently were prepared for the determination of radioactivity by placing each specimen in haematocrit tubes, 8 mm. in diameter, and centrifuging at 3,000 revolutions per minute (r.p.m.) for 40 minutes. The plasma was then removed, being replaced by an equal volume of distilled water, and haemolysis accomplished by inverting or gently shaking the tube. Of the haemolysate 1 ml. was placed on a "pyrex" watchglass and allowed to dry. The samples were counted with a Geiger–Müller counter. The value for the total circulating blood could then be determined by calculation. For estimation of red-cell and plasma volumes the use of the haematocrit value was necessary, together with the figures for radioactive phosphorus. In the majority of cases the values obtained with radioactive phosphorus were lower than those obtained by the dye or carbon monoxide method. Blood volume was determined by the radioactive phosphorus technique in 5 patients with hypoproteinaemia. The results varied, and few inferences could be drawn from them; the procedure was, however, fairly simple and well tolerated.

The second method of measuring blood volume, by means of plasma and albumin injections, was employed in patients suffering from malnutrition, hypoproteinemia, and oedema. The procedure was based on the changes in haematocrit value and plasma albumin level after injection of a known amount of albumin, either as salt-poor human albumin (25%) or as double-strength plasma. Samples were collected before and after the injection. Fractionation was carried out by the method of Campbell and Hanna. Total and fractional protein estimations were made by the colorimetric method of Weichselbaum. From these determinations the plasma volume of the total circulating blood could, by calculation, be known. This method gave values which were usually 500 to 600 ml. higher than those obtained by the radioactive phosphorus method. Changes in blood volume, however, showed complete correlation between the two procedures. The authors consider the radioactive phosphorus method to be as accurate as any now available and more convenient for routine use than many of them. They consider also that it might be of clinical value in the study of patients suffering significant alteration in the blood volume or its constituents.

R. P. Foggie

2237. **Fractionation of Serum into Albumin and α-, β-, and γ-Globulin by Sodium Sulfate**

A. C. KIBRICK and M. BLONSTEIN. *Journal of Biological Chemistry* [*J. biol. Chem.*] **176**, 983–987, Nov., 1948. 10 refs.

In these experiments fractionation was achieved by adding 0·5 ml. of serum or plasma to 10 ml. of 15·75, 19·90, and 27·20% sodium sulphate at 37° C.; 10 mg. of "hyflo super-cel" was added and the mixtures were allowed to stand at 37° C. for one hour. The first sodium sulphate solution precipitates γ-globulin, the second β-globulin, and the third precipitates the rest of the globulin fraction. The protein content of the filtrates was determined by the biuret method. To check the accuracy of this salt–fractionation method the albumin–globulin separation was determined by precipitation with cold methanol; electrophoretic determinations of the globulin fractions were also carried out, and the γ-globulin fraction was determined by the use of immune rabbit sera. There is good agreement between the salt-fractionation method and the various methods used for controlling the procedure.

J. Dawson

NUTRITION AND DIGESTION

2238. **Further Observations on the Nutritive Value of the Proteins contained in Wheat Flours of Different Extraction Rates**

H. CHICK and E. B. SLACK. *British Journal of Nutrition* [*Brit. J. Nutrit.*] **2**, 205–213, 1948. 2 figs., 24 refs.

Groups of 6 litter-mate rats of 45 g. initial weight were fed for seven weeks on diets the protein of which was suboptimal for normal growth and was derived entirely from wheat flours of 70, 80, 85, and 100% extraction, respectively, from the same grist. The growth rates accorded consistently with the extraction rate, and the increase in weight per gramme of protein consumed, and

the percentage of nitrogen consumed which was retained, were significantly higher for the higher-extraction flours. In other tests it was found that, to obtain the same rate of growth with 70% extraction flour as with 100% extraction, the protein of the former had to be increased by 30%. The digestibility coefficient was about 89 for 70% extraction and 81 for 100% extraction flours. The values for 80% and 85% were intermediate. *H. E. Magee*

2239. **Composition of Rats Fed on Diets containing Wheat Flours of Different Percentage Extraction**
E. B. SLACK. *British Journal of Nutrition* [*Brit. J. Nutrit.*] **2**, 214–220, 1948. 1 fig., 6 refs.

In these analyses, carried out to confirm the findings reported in the previous paper (Abstract 2238), the bodies of the four groups of rats were analysed at the close of the experiment for water, fat, protein, and ash, and the results compared with the analyses of litter-mate rats killed at the start of the experiment. The comparisons supported these findings and showed that the greater nutritive value of the higher-extraction flours more than compensated for the lower digestibility. The gain in protein was proportional to the gain in body weight, and as the weight increased so did the fat, but the water content declined. *H. E. Magee*

2240. **Comparison of Nutrient Values of Individual Diets Found by Calculation from Food Tables and by Chemical Analysis**
E. R. BRANSBY, C. G. DAUBNEY, and J. KING. *British Journal of Nutrition* [*Brit. J. Nutrit.*] **2**, 232–236, 1948. 3 refs.

This investigation was undertaken to test the reliability of tables of food composition for the calculation of the nutrient contents of diets. Over a period of three days 33 selected persons of both sexes carefully weighed all the foods they consumed and also duplicates. The duplicates were put in watertight jars and kept in refrigerators and then analysed for moisture, ash, calcium, iron, nitrogen, fat, sugar, and starch. The totals of these as calculated from food tables were compared with those obtained by analysis. The average value by calculation was higher by 2% for calories and by 5% for fat and carbohydrate, and lower by 10% for protein and 7% for calcium. The greatest divergence was for iron, which was 38% lower by calculation. Except for iron, it is considered that the agreement is good enough for practical purposes. The 33 participants were all scientifically trained, and several were research workers.
H. E. Magee

2241. **The Relative Biological Values of the Proteins in Cereal Grains**
B. SURE and F. HOUSE. *Journal of Nutrition* [*J. Nutrit.*] **36**, 595–600, Nov. 10, 1948. 10 refs.

The experimental ration, which consisted of a protein-free basal diet, adequate in minerals and vitamins A, D, and E, and with added B-complex vitamins, and the cereal grain to furnish 5% protein, was fed to equivalent groups of rats: approximately 8 rats for the study of each cereal grain. The nitrogen balances were determined over a preliminary 7-day period on an egg standardizing ration, and, with a pre-test interval of 3 to 5 days on the experimental rations, over the test period of 7 days on the experimental rations. The biological values of the proteins of the cereal grains, as expressed by the percentage of the absorbed nitrogen which is retained in the body, were as follows: milled grains—rice 79·0, wheat 63·5, rye 69·7, maize 36·2; whole grains—rice 85·1, wheat 83·0, rye 80·4, maize 84·7, rolled oats 82·1. The net values for utilization of protein (biological value × coefficient of digestibility ÷ 100) were: milled grains—rice 75·1, wheat 60·0, rye 63·1, maize 32·0; whole grains—rice 80·0, wheat 76·1, rye 73·2, maize 78·8, rolled oats, 75·6.

Thus, of the milled grains, the maize was by far the poorest source and the rice the best; on the other hand, there were no noticeable differences in the protein values of the whole grains. The rats which received whole maize consumed about 40% less of the rations than those which received milled maize, but the former utilized their proteins more than twice as well. It is suggested that the maize receives too drastic treatment in the course of being milled; apparently too many bran layers, which carry lysine and tryptophan, the amino-acids most deficient in the maize kernel, are removed. *Joseph Parness*

2242. **The Effect of Previous Diet on the Ability of Animals to do Work During Subsequent Fasting**
L. T. SAMUELS, R. C. GILMORE, and R. M. REINECKE. *Journal of Nutrition* [*J. Nutrit.*] **36**, 639–651, Nov. 10, 1948. 1 fig., 11 refs.

Male rats were placed in "combined" activity and metabolism cages, as designed by Reinecke, and were fed for a preliminary period on a stock diet of calf meal *ad libitum*, during which records of voluntary activity were kept. The rats were then given one of the following diets: (*a*) fat = 80% of total calories; (*b*) carbohydrate = 77·8% of total calories; (*c*) protein = 92·4% of total calories. In diets *a* and *b* sufficient protein was included to maintain an adequate supply of amino-acid. The diets were given by stomach-tube in equicaloric amounts, usually 52 Calories daily. After 4 weeks of feeding on the experimental diets the rats were fasted, and exhaustion tests were then begun within 1 to 4 days and repeated every 7 days until the rats died. Voluntary activity was recorded during the feeding period and during the intervals between exhaustion tests. Nitrogen balances were determined during the feeding and the fasting periods.

It was found that voluntary activity dropped to approximately one-half of the previous rate when the change was made from the calf-meal diet or force-fed mixed diet to any of the experimental diets. During fasting the rats which had received the high-fat diet gave the best performance in exercise tests, the carbohydrate-fed the next, and the protein-fed the poorest; a longer time was required for exhaustion by the surviving rats, especially by the carbohydrate-fed group, in the second exercise test than in the first. Voluntary activity

during fasting was less in the fat-fed rats than in either of the other groups; in consequence the total activity of the fat-fed group during fasting did not differ significantly from that of the carbohydrate-fed group. The fat-fed group survived the longest (average 18·3 days), the carbohydrate-fed were next (average 15·5 days), and the protein-fed had the shortest survival time (average 10·2 days). There were significant differences in the blood-sugar levels of the groups during the fasting period, the carbohydrate group starting off with a significantly higher level than that of the other two groups, but reversing within 16 hours to a significantly lower level, so that the difference was still 12 mg. per 100 ml. at the end of 4 days of fasting and highly significant statistically; the fat-fed group showed a considerable increase in the blood-sugar level during exercise, the average increase being 26·5 mg. per 100 ml., while the other two groups showed only small and irregular differences after exercise. In the first 4 days of fasting the fat-fed group excreted significantly less nitrogen and the protein-fed group significantly more nitrogen than the carbohydrate-fed; also, the fat-fed group excreted less nitrogen during the exercise periods, the nitrogen output per unit of work being definitely lower.

It is concluded that the differences in exercise performance and in survival could be accounted for partly on the basis of differences in the metabolic mixture burned by the various groups during the phases of the experiment, and also, in the case of the fat-fed rats, by the reduced amount of voluntary activity during fasting.

Joseph Parness

2243. **The Basal Metabolism of Two Hundred and Eighteen Girls and Young Women of Southern Arizona, Fourteen to Twenty-three Years of Age, Inclusive**

E. M. THOMPSON, E. W. COX, and A. M. RIDGWAY. *Journal of Nutrition* [*J. Nutrit.*] **36**, 507–517, Oct. 11, 1948. 1 fig., 18 refs.

The present study was made in southern Arizona during the years 1940 to 1947 in the winter months between October and April, being based on 887 individual determinations of basal metabolism on 218 girls and young women from 14 to 23 years of age, inclusive. Two 8-minute to 10-minute tests were made on each of two or more mornings, until oxygen consumption in c.c. per minute in either of the tests on a given day agreed within 5% with the consumption on another day. In calculating the Calories per square metre per hour, the results obtained by the following 4 methods were compared: (1) the 5% check, as described above; (2) average of all accepted tests; (3) accepted first tests only; (4) average of accepted tests on the first morning only.

The yearly means, obtained by all 4 methods, showed a steady drop year by year for the first 5 years; the lowest yearly means, as was to be expected, were obtained by the first method, being 36·22, 34·37, 33·12, 32·12, 31·21, 31·12, 31·14, 31·30, 30·84, and 30·79 Calories per square metre for each age-group from 14 to 23, respectively. Smoothed means for the first 5 years (deduced by reduction of the data to linear form) also showed a consistent fall in Calories year by year by all 4 methods; the smoothed yearly means obtained by the first method dropped from 36·40 for the 14-year-old group to 31·21 for the 18-year-old group; the best straight-line fit was obtained by means of the second method and the next best by the first; no statistically significant differences were found on comparison of the respective yearly means obtained by each of these 2 methods, although those by the first were lower in each case; variability around the means was less by the second method; correlation with age was found to be highly significant statistically by the first 2 methods and less significant by the other 2. Lumped means for the years 18 to 23, inclusive, were 31·1 by the first method and 31·5 by the second method.

It is noted that southern Arizona is situated in the area of the U.S.A. which has the most sunshine and the least relative humidity; the mean annual temperature for 1934–8, inclusive, was 67·2° F. (19·6° C.). The basal metabolism of the younger subjects in the present study is fairly close to that of some subjects in studies reported from higher latitudes, but from about the middle of the fifteenth year it rapidly approaches a much lower level. When the 18-year-old group was compared with similar groups of the same age reported from 5 mid-western States, a diminishing metabolism was observed with increasing mean annual temperature. The low energy level beginning at the eighteenth year would seem to indicate the appearance of the chemical regulation mechanism in women in warm environments which has also been demonstrated by the direct method of calorimetry. The present study was made at an altitude of 2,400 feet (720 m.); the results therefore do not support the view that altitude *per se* tends to increase basal metabolism. The authors consider that, for results presented in the form of age-group averages, the first two methods of evaluating individual tests are most suitable.

Joseph Parness

2244. **Tissue Changes and Sodium Balance in Pantothenic Acid-deficient Rats**

A. J. MCQUEENEY, L. L. ASHBURN, F. S. DAFT, and R. FAULKNER. *Endocrinology* [*Endocrinology*] **41**, 441–450, Dec., 1947. 32 refs.

Adrenal cortical function in relation to salt and water metabolism in pantothenic-acid deficiency was studied in 42 Sprague–Dawley rats 21 to 24 days old and weighing 30 to 45 g. Three groups of 6 rats were kept on a diet deficient in pantothenic acid, one on a riboflavin-deficient diet; of the three remaining groups one was used for pair-fed controls, one received a diet restricted to 2 g. per rat per day 8 days before the end of the experiment, and the third consisted of controls given food *ad libitum*.

All rats received 0·145% NaCl solution, in graduated tubes, to drink until, after 32 days on diet, they were placed in metabolism cages for 5 days. During the first 3 days of this period NaCl was replaced by distilled water. Twenty-four-hour urine samples were collected and intake of food and fluid was measured during this period.

The weights of the deficient animals and their pair-fed controls were the same until the twenty-fifth day, when

the former lost weight. Sodium determinations by means of the flame photometer revealed no significant difference in sodium conservation in deficient animals, compared with those treated with 1·5 mg. per day of desoxycorticosterone (DOCA) or 1 mg. per day of calcium pantothenate subcutaneously during the 5-day metabolism period, or with controls. Similarly there was no significant difference in fluid intake or in adrenal and spleen weights. There was cortical depletion of lipid in the pantothenic-acid-deficient animals, the glomerulosa being normal but varied amounts of depletion being noted in the fasciculata. The distribution of the acetone–alcohol-soluble, phenylhydrazine-positive material was paralleled by that of the sudanophilic material, but not by the bi-refringent material, which, however, was also reduced in amount. This arrangement could not be seen in the riboflavin-deficient rats and could be restored to normal in the pantothenic-acid-deficient groups by treatment with pantothenic acid, even when diet was restricted to 3·5 g. per rat per day. The decrease in thymus weight found in pantothenic-acid deficiency was not specific, as a similar reduction was observed in riboflavin-deficient rats, a somewhat smaller reduction also being noted in the pair-fed controls. Thymus weight was increased by pantothenic acid but not by DOCA. Histologically in the two deficient groups there were loss of lymphoid tissue and persistence of reticulo-endothelial and epithelial elements, the picture being restored to normal in animals receiving pantothenic acid. The lymph nodes shrank in size and primary follicles diminished in size or disappeared. These changes were not apparent in the other groups and were reversed by treatment with pantothenic acid but not with DOCA. The latter was similarly unsuccessful in restoring cartilaginous and osteoblastic activity in the femoral and tibial epiphysial plates of the deficient groups. The authors conclude that sodium balance was not affected in pantothenic-acid deficiency, although a mild adrenal insufficiency may have been present. The changes found in the adrenals, lymph nodes, and thymus confirm those observed by other authors, but no light has been thrown on the reason for thymus atrophy.

S. A. Simpson

2245. **Deficiency of Vitamin A in University Students**
S. Doraiswami and J. Yudkin. *British Medical Journal* [*Brit. med. J.*] **2**, 708–710, Oct. 16, 1948. 12 refs.

Using the Crookes adaptometer the authors plotted the dark-adaptation curves in 71 women students; 52 of the students were then given large supplements of vitamin A for 8 to 14 days, while the other 19 took capsules containing arachis oil. At the end of this period the curves were again plotted, and were taken to indicate a significant improvement if the final rod threshold decreased by more than 0·15 micromicrolambert. Of the students receiving supplementary vitamins 9 showed such an improvement; there was no change in the 19 controls.

In October, 1946, and November, 1947, the average daily intake of vitamin A during one week of 34 students was determined by various methods: 7 of these students were found to take less than 2,500 i.u. daily. The quantities of carotene were divided by three to give the equivalents of vitamin A. Thirteen students took part in both investigations. In 10 of them the daily intake of vitamin A was over 3,000 i.u. and their dark-adaptation showed no improvement after the vitamin supplements; 3 took slightly less than 2,500 units daily, and there was a significant improvement in the dark-adaptation curve for these 3 students after the supplementary doses.

H. E. Harding

2246. **The Extrahepatic Conversion of Carotene to Vitamin A**
R. F. Krause and H. B. Pierce. *Archives of Biochemistry* [*Arch. Biochem.*] **19**, 145–148, Oct., 1948. 5 refs.

Vitamin A levels in serum were studied 6 to 8 hours after oral feeding of 20,000 i.u. of carotene to normal rats and to those in which the liver had been removed from the general circulation. This operation was effected by partial ligation of the portal vein to stimulate development of collateral circulation, and 10 days later tying off the portal vein, hepatic artery, and common bile duct. Intracardiac injection of indian ink showed the hepatic circulation in the "ligated" rats to be 10% of that in normal animals. Blood samples were taken by cardiac puncture. In both normal and "ligated" rats there was a rise in vitamin A level in serum after carotene feeding, with no such increase in "ligated" rats to which no carotene had been given. This indicates that conversion to vitamin A occurs in both series.

J. Dawson

2247. **Niacin Deficiency Anemia in Swine**
G. E. Cartwright, B. Tatting, and M. M. Wintrobe. *Archives of Biochemistry* [*Arch. Biochem.*] **19**, 109–118, Oct., 1948. 5 figs., 11 refs.

The production is demonstrated of a normocytic anaemia in weanling pigs on a low-protein (10% casein) diet deficient in nicotinic acid, after a period of 60 to 120 days. The anaemia was completely corrected by the administration of nicotinic acid or by raising the protein level to 26%, although both additions were required for a resumption of normal growth. Repeated nicotinic acid depletion over a period of 216 days did not lead to the production of a deficiency of the anti-pernicious-anaemia factor.

J. Dawson

2248. **Significance of the Beta Granules in the Islets of Langerhans of the Pancreas**
S. S. Barron. *Archives of Pathology* [*Arch. Path.*] **46**, 159–163, Aug., 1948. 2 figs., 2 refs.

It is known that in rats procedures which reduce insulin requirements, such as starvation, feeding on a purely fat diet, or daily injections of insulin, diminish the insulin content of the pancreas. The author shows that these procedures reduce the number of granules in the β cells of the pancreatic islets, and concludes that the granules represent a precursor of insulin.

Martin Hynes

Pharmacology and Therapeutics

2249. **Response of the Duodenum to Morphine**
T. A. Loomis. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 146–150, Oct., 1948. 3 figs., 14 refs.

The author carried out experiments on the duodenum of the dog to determine the muscular response of the intestinal wall to intravenous injections of morphine sulphate. The animals were anaesthetized, and the stomach and duodenum exposed through an abdominal incision. Simultaneous graphic recordings were made of the activity of the circular and longitudinal muscles of a segment of the duodenum after incising the stomach wall; the circular-muscle movements were recorded by means of a balloon inserted into the duodenum through the pyloric sphincter. The longitudinal-muscle activity was recorded by Jackson's internal-organ apparatus, which was sutured to the mucosal surface. The drugs given were injected into superficial branches of the femoral vein.

Repeated equal doses of morphine sulphate were found to diminish muscle activity; only one injection of the drug, therefore, was given to each animal in the experiments described. The most frequent response to varying amounts of morphine sulphate was an immediately increased activity of the circular muscle and a simultaneous decrease in the activity of the longitudinal muscle. Exceptions were occasionally seen, particularly in the case of the longitudinal muscle. The increase in activity of the circular muscle resulting from a morphine injection was not abolished by atropine. The type of response of the duodenum to morphine appeared to be independent of the amount given and of the original state of activity of the muscle wall. *R. P. Foggie*

2250. **Clinical Experience with Methadon (Dolophine)**
A. C. Kirchhof and N. A. David. *Anesthesiology* [*Anesthesiology*] **9**, 585–593, Nov., 1948. 2 figs., 26 refs.

This is a clinical report on the drug (6-dimethylamino-4 : 4-diphenyl-3-heptanone) called "amidone" in Germany and "dolophine" in the U.S.A. It is now officially known as methadon.

Though resembling neither structurally, its properties place it somewhere between morphine and pethidine—rather nearer the former in that it causes some vagal slowing and fall in blood pressure with respiratory depression but has less spasmolytic effect than pethidine. It is about 2½ times as toxic as the latter drug but is much more potent. It appears to be less effective under clinical conditions than in laboratory experiments. Its clinical effect has been studied and classified in 2,860 administrations. It was initially used in doses of 5 mg., but the best effects were observed with doses of 10 to 15 mg., which is the range in which the dose of morphine usually lies. In 2·5-mg. doses orally it has been useful (in a linctus) as a cough sedative. It causes some unpleasant reactions, notably nausea, but this trial does not indicate that these are serious. Patients develop tolerance to very frequently repeated doses, so it is presumed that addiction is a possibility though unlikely, since the drug does not produce noticeable euphoria. The nausea referred to occurred most commonly in ambulant patients receiving the drug orally. *John Challis*

2251. **The Effect of Barbiturates and Other Substances on Motion Sickness in Dogs**
R. L. Noble. *Canadian Journal of Research* [*Canad. J. Res.*] Sect. E **26**, 283–294, Oct., 1948. 4 refs.

A large number of barbiturates were given by mouth to dogs, which were subjected to the motion of swinging 2 to 4 hours later. The results are tabulated, but accurate comparisons are difficult because of the great individual differences among the dogs. The most effective drug was ethyl-1 : 3-dimethylbutylbarbituric acid, which was much more potent than the ethyl-β-methylallylthiobarbituric acid used as standard in earlier experiments ("V–12"). Hyoscine in a dose of 0·43 mg. was ineffective. Where sufficient barbiturate was administered to give protection, the latter lasted for 18 to 24 hours; protection depended on the total dose, whether this was single or divided. *V. J. Woolley*

2252. **Enzymic Hydrolysis of Morphine Esters**
S. Ellis. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **94**, 130–135, Oct., 1948. 3 figs., 12 refs.

The author has shown that three separate enzymes are responsible for the hydrolysing activity of the plasma and liver of some rabbits on monoacetylmorphine, benzoylcholine, and atropine. The investigations were carried out *in vitro* by the conventional Warburg manometric technique with heparinized blood plasma and serum and washed liver homogenates. Of samples of plasma from 17 rabbits, 7 had negligible hydrolytic activity on monoacetylmorphine, atropine, or benzoylcholine. The monoacetylmorphine esterase of rabbits' blood was found only in the plasma, and human, dog, sheep, and guinea-pig sera were devoid of this activity. Physostigmine, neostigmine, and tetraethylpyrophosphate (TEPP) were found to be inhibitors of the esterases. After inactivation of sera with TEPP all three activities were recovered at the same rate. Liver damage induced by intraperitoneal injections of carbon tetrachloride did not differentially depress the several enzymes of rabbits' plasma. Separation of the atropine esterase from the other two activities was effected by precipitation of liver globulin by half-saturated ammonium sulphate, when the atropine esterase was completely inactivated by incubation at 48° C. for one hour. At the same time mono-

acetylmorphine esterase was reduced 50% and benzoylcholine esterase 30%. The relative activities of benzoylcholine and monoacetylmorphine esterases of guinea-pig liver could be altered by drying with acetone. The author has confirmed that cholinesterases are not the enzymes responsible for the hydrolysis of heroin. He also found that acetylsalicylic acid is hydrolysed rapidly by guinea-pig plasma, but only slowly by plasma from man, rabbits, and dogs, the enzyme responsible not being the one which hydrolyses heroin. The hydrolysis of the 3-acetyl group of heroin appeared to be a function of tributyrinase. *G. F. Somers*

2253. **Treatment of Cardiac Disorders by Hellebrin, a Glycoside of Hellebore.** (Du traitement des affections cardiaques par l'hellébrine, glucoside de l'ellébore)
W. LÖFFLER, A. F. ESSELLIER, and A. PEDRAZZINI. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 1021–1025, Oct. 23, 1948. 4 figs., 19 refs.

This article reports observations on the effect of "helborside" in 71 patients with congestive heart failure. Helborside is an aqueous solution of hellebrine, one of two glycosides isolated by Karrer from the roots of *Helleborus niger melampodium*. Its formula is $C_{36}H_{52}O_{15}$; the structural formula is that suggested by Schmutz (*Pharm. Acta Helvet.*, 1947, **22**, 373). The literature since Löffler's communication in 1936 on the effect of hellebrin is briefly reviewed. A test dose of 0·1 mg. is first given, after which the daily amount, given intravenously in a single dose, is rapidly increased to 0·5 mg., the average dose being 0·3 to 0·5 mg. and the maximum dose 0·7 mg. Daily injections are continued until the desired effect is attained, usually within 8 to 15 days, provided no signs of overdosage occur; these are the same as with digitalis. Subsequently treatment is continued by 2 to 3 injections a week, or by digitalis given orally. Satisfactory results were obtained, in some cases after digitalis treatment had been unsuccessful. Slowing of the heart rate is one of the most notable effects, irrespective of the underlying rhythm; it is also observed in cases of sinus tachycardia due to hyperthyroidism or infections, and is particularly pronounced in auricular fibrillation. Lengthening of auriculoventricular conduction time, dropped beats, and occasionally complete auriculo-ventricular block were seen. A considerable increase in diuresis was observed in some cases. The indications for interrupting treatment are the same as with digitalis. In respect of rapidity of action and duration of effect, helborside stands midway between strophanthin and digitalis. *A. Schott*

2254. **Hitherto Undescribed Neurological Manifestations of Digitalis Toxicity**
R. C. BATTERMAN and L. B. GUTNER. *American Heart Journal* [*Amer. Heart J.*] **36**, 582–586, Oct., 1948. 11 refs.

Neurological manifestations of digitalis poisoning are more common than is generally thought. In a series of cases approximately 41% of toxic symptoms pointed to the involvement of the central or peripheral nervous system. Neuralgic symptoms (usually involving the lower third of the face) occurred in approximately 9% of patients receiving a toxic dose of a digitalis preparation. Neurological symptoms may be the earliest, the most severe, and the sole manifestations of digitalis intoxication. *R. T. Grant*

2255. **Effects of a Liver Extract (Cortunon) on Coronary Flow in the Rabbit's Heart.** [In English]
K. I. MELVILLE. *Revue Canadienne de Biologie* [*Rev. canad. Biol.*] **7**, 491–507, Nov., 1948. 14 refs.

"Cortunon" is a commercial liver extract preparation, known in Germany since 1928 as "eutonon". Several workers have reported that cortunon increases coronary flow, a finding which the author confirms. Single injections of 0·1 or 0·2 ml. of a 7·5% solution induced a rapid and intense coronary dilatation in the isolated perfused rabbit heart (Langendorff–Stehle preparation). The effect was extremely transient, however, and was associated with a slowing of the heart rate. Even adrenaline had a more sustained coronary dilator action when tested under the same conditions. These results "do not in any way signify that this extract is of any therapeutic value as a coronary dilator drug". *F. N. Fastier*

2256. **The Effect of Sodium Salicylate Upon Serum Disease in Rabbits**
K. SMULL, R. W. WISSLER, and J. M. WATSON. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 936–950, Aug., 1948. 6 figs., 41 refs.

The therapeutic effect of sodium salicylate on experimental serum sickness in rabbits was investigated. The arterial blood pressure, erythrocyte sedimentation rate, salicylate concentration in blood, formation of antibodies to injected horse serum, red cell volume, and tissue histology were studied.

The following results were obtained. The erythrocyte sedimentation rate (E.S.R.) was increased in many of the animals with serum sickness, after due correction for anaemia had been made. Though there was some correlation between rise in E.S.R. and the development of lesions, this was not constant. Salicylate treatment had no effect on the E.S.R. Intravenous horse serum (10 ml. per kg.) produced an anaemia in most animals. Salicylates appeared to intensify this. No morbid change was observed in arterial blood pressure in the animals. Attempts to maintain salicylate levels at 250 μg. per ml. of blood were made difficult in the rabbit by the appearance of toxic symptoms, some of the animals dying of salicylate poisoning. Serum sickness in the rabbit produced: (1) Arteritis, not always found, but when present affecting the medium-sized arteries of heart, lungs, pancreas, stomach, liver, kidney, adrenal, testis, uterus, and diaphragm. (2) Proliferative lesions at the bases of aortic and mitral valves. (3) Many small areas of necrosis in the myocardium, one of the surprising features of which was an absence of inflammatory reaction. (4) In the kidney, a proliferation of cells of the juxta-

glomerular apparatus was sometimes seen, together with a variable lymphocytic infiltration. No changes attributable to salicylate poisoning were seen, and it was concluded that salicylates decreased the lesions due to serum sickness. Antibody titres were higher in the untreated animals than in those receiving salicylates, except for one animal in each group. The series is too small for critical analysis. *J. D. Judah*

2257. **Histaminaemia after "Sympatol".** (Histaminämie nach Sympatol)
H. BAUR and H. STAUB. *Helvetica Physiologica et Pharmacologica Acta* [*Helv. physiol. pharmacol. Acta*] **6**, C 14–15, 1948. 5 refs.

It has been previously shown that slow intravenous injection of 0·2 mg. of adrenaline in human subjects produces in most instances a significant rise in plasma histamine concentration which can be diminished or prevented by "antistin" (Staub, *Helv. physiol. pharmacol. Acta*, 1946, **4**, 539). Similar experiments were made with a synthetic sympathomimetic, "sympatol", of which 0·12 g. in 20 ml. of saline was slowly injected intravenously, the injection taking 10 minutes. In 32 of 40 experiments (in 35 subjects free from allergic or vegetative disorders) there resulted a significant increase in plasma histamine concentration of 2 to 5 times the initial value. Subjective complaints—slight palpitation, feeling of cold or heat, pressure in the head, and nausea—were more pronounced with adrenaline than with sympatol. The increase in plasma histamine concentration lags behind the maximum rise in blood pressure, and this interval is longer with sympatol than with adrenaline.

In experiments with adrenaline in rabbits a rise in the plasma histamine level occurred in 7 out of 12, and with sympatol in 22 out of 25 instances, and in the latter a threefold to fivefold increase was common. Control experiments with normal saline did not produce any change. The histaminaemia following injection of sympatol is considered to represent a physiological mechanism of counter-regulation similar to that assumed for adrenaline. *H. Pollak*

2258. **The Comparative Pharmacology of *p*-Fluorophenethylamine and *p*-Fluorophenethyl-methylamine**
D. F. MARSH. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **94**, 192–196, Oct., 1948. 2 figs., 14 refs.

In this paper the influence of a fluorine atom introduced into the *para* position of the benzene ring in phenethylamine structures has been studied. The compounds *p*-fluorophenethylamine and *p*-fluorophenethyl-methylamine were compared with the corresponding unsubstituted amines, and with tyramine, in which the *para* position is occupied by an –OH group. Blood-pressure effects were studied by conventional methods in intact dogs, cats, rabbits, and rats under pentobarbitone soluble anaesthesia. Rabbits proved unsatisfactory. The fluorine atom increased the pressor activities of these compounds, but the substances were still not as active as tyramine. On a molecular basis their activity was about one-hundredth that of adrenaline. Except in one single instance they had a depressant effect on the perfused heart, whereas tyramine had a stimulatory action. The phenethylamine compounds did not produce bronchodilatation in guinea-pig lungs or antagonize the action of histamine. The phenethylamine compounds caused contraction of the isolated rabbit jejunum, and this activity was increased by fluorine substitution, but they were not as active as tyramine. At the same time they often diminished tone. Therefore the replacement of the hydrogen atom in the *para* position of phenethylamine and phenethyl-methylamine by a fluorine atom increased the sympathomimetic actions; neither of these substances was as active as tyramine. *G. F. Somers*

2259. **The Effect of Quinine on the Nervous System.** [In English]
J. TEN CATE and J. T. F. BOELES. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **77**, 468–476, Nov. 1, 1948. 3 figs., 13 refs.

This account of work done in the physiology laboratory of the University of Amsterdam shows that the electrical activity of the cerebral cortical cells of rats is reduced by intraperitoneal injection of 10 or 15 mg. of quinine chloride per kg. It was first confirmed that tubocurarine, pentobarbitone soluble, thiopentone soluble, or a low external temperature causes a fall in the rectal temperature of the rat. The electroencephalogram (EEG) was not significantly affected until the animal's rectal temperature fell below 32° C.

In anaesthetized or curarized rats, quinine caused a fall in rectal temperature to 33° C., and reversible EEG changes were noted. When curarized rats were kept at an external temperature of 30° C., quinine lowered the rectal temperature only by about 0·5° to 1° C., but small alterations in the EEG were again observed. The direct effect of quinine on the electrical activity of the cortical cells is relatively small when such non-toxic doses of up to 15 mg. per kg. are used. Quinine did not significantly alter the chronaxie of the sciatic nerve of the anaesthetized rat. *Derek R. Wood*

2260. **Cholinesterases, Cholinergic Symptoms, and Sensitivity to Acetylcholine.** (Cholinestérases, symptômes cholinergiques et sensibilité à l'acétylcholine)
C. HEYMANS, R. VERBEKE, and Z. VOTAVA. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **77**, 486–494, Nov. 1, 1948. 4 figs., 18 refs.

The fall in blood pressure, the bradycardia, and the hyperpnoea which follow the intravenous injection of 0·5 to 1 mg. of acetylcholine hydrochloride in anaesthetized dogs are much increased after injection of hexaethyltetraphosphate (HETP), tetraethylpyrophosphate (TEPP), or the dimethylcarbamate of (2-hydroxy-5-phenylbenzyl)trimethylammonium. *In vitro* tests confirmed that these three substances almost completely inhibited the pseudo-cholinesterase activity of the blood without affecting its true cholinesterase activity. No

cholinergic reactions followed injection of these substances and it is concluded that pseudo-cholinesterase plays an essential part in the *in vivo* breakdown of acetylcholine. *Derek R. Wood*

2261. **Modification of the Vascular Effects of *iso*-Propyladrenaline and Adrenaline by Ergotamine.** (Recherches sur les modifications apportées par l'ergotamine aux effets vasculaires de l'*iso*propyladrénaline et de l'adrénaline)
R. HAZARD, M. BEAUVALLET, and R. GIUDICELLI. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **77**, 504–508, Nov. 1, 1948. 2 figs., 4 refs.

Experiments reported from the Pharmacology Laboratory of the Faculty of Medicine of Paris indicate that the musculotropic action of ergotamine is important in determining the inversion by this substance of the hypotensive effect of *iso*propyladrenaline in vagotomized dogs anaesthetized with chloralose. This effect of ergotamine is paralleled, or can be added to, by posterior pituitary extract, which stimulates smooth muscle; the reversal effect of both these substances is inhibited, partly or completely, by papaverine, a smooth muscle relaxant. The dose of ergotamine (about 1 mg.) used in all these experiments does not appreciably affect the pressor action of adrenaline. Neither barium nor magnesium chloride influences this reversing action of ergotamine, although large doses of barium chloride suppress the normal effects of adrenaline and *iso*propyladrenaline on blood pressure. *Derek R. Wood*

2262. **Results of Application of Ergotamine to the Vomiting Centre.** (Application d'ergotamine sur le bulbe émétisant)
J. CHEYMOL and A. QUINQUAUD. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **77**, 509–512, Nov. 1, 1948. 8 refs.

Direct application of ergotamine tartrate or dihydroergotamine to the vomiting centre of dogs prevents the stimulation of vomiting by substances such as apomorphine, which act centrally after injection, but does not suppress the reflex vomiting due to such salts as zinc sulphate given by mouth. Ipecacuanha powder given orally does not cause vomiting if ergotamine has been applied to the vomiting centre, the central effect of the absorbed emetine being suppressed. After ergotamine, tartar emetic still causes vomiting if given orally but not if given intravenously. This effect of ergotamine permits distinction between central and reflex stimulation of the vomiting centre. *Derek R. Wood*

2263. **New Indications for the Use of Curare in Pathological Conditions.** (Indications nouvelles d'utilisation du curare en pathologie)
H. LABORIT and H. TANGUY. *Thérapie* [*Thérapie*] **3**, 1–9, 1948. 3 refs.

Cholinergic nerves may be subdivided into: (1) Central cholinergic fibres which act either on voluntary muscles or on autonomic ganglia, whether sympathetic or parasympathetic; these fibres are said to have a nicotinic action and are antagonized by curare. (2) Fibres which arise in peripheral parasympathetic ganglia; these have a muscarine action and are antagonized by atropine. It is argued that by associating eserine with curare in doses below those which act on voluntary muscles, only the muscarine action of the cholinergic fibres persists. This in effect amounts to a physiological section of the sympathetic system. Various conditions which would benefit from lumbar sympathectomy have been treated in this way. These include 4 cases of essential hypertension and single cases of arteritis of the legs and of megacolon. Good results are claimed. *J. F. Delafresnaye*

2264. **Action of Acetylcholine, Histamine, and Cholinesterase Inhibitors on Isolated Ileum in Relation to its Survival Time**
P. FLESCH and E. KUN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 166–169, Oct., 1948. 4 figs., 8 refs.

In tests on the isolated ileum of the guinea-pig, rat, rabbit, and chicken it has been shown that about 2½ to 3 hours after the death of the animal histamine fails to reinforce a contraction due to acetylcholine, as it did previously. Further, atropine then no longer blocks the action of acetylcholine and of the cholinesterase inhibitors, eserine, neostigmine, and hexaethyltetraphosphate (HETP). Rat, rabbit, and chicken ileum also fail to be contracted by histamine at this time, though still responding to acetylcholine. The theory that histamine is acting by liberating acetylcholine is not supported.

[Atropinized guinea-pig ileum is a standard preparation for estimation of histamine in extracts. It is important, as the authors note, to realize that 2½ to 3 hours after the animal's death the tissue may partly regain its response to acetylcholine, even when suspended in atropine–Tyrode solution.] *Derek R. Wood*

2265. **Local Anaesthetic Action of Some Synthetic Antihistamine Drugs. Relation Between Anaesthetic and Antihistamine Actions.** (Pouvoir anesthésique local de quelques antihistaminiques de synthèse: relation entre l'action anesthésique et l'action antihistaminique)
B. N. HALPERN, G. PERRIN, and P. B. DEWS. *Semaine des Hôpitaux de Paris* [*Sem. Hôp. Paris*] **24**, 2561–2564, Oct. 26, 1948. 7 figs., 6 refs.

The sensitivity to touch of the cornea was used to test the anaesthetic action of various antihistamine drugs. The cornea of a rabbit was stimulated by being touched with a hair at a rate of 100 times per minute, and the number of stimulations required for the appearance of the corneal reflex was noted. Drops of the liquid to be tested were instilled, and the action was compared with that of 1% cocaine. It appeared that the anaesthetic action increased with the concentration of the antihistamine used. The action of "antergan" was comparable with that of cocaine, while the action of "3,277 R.P." ("phenergan") was stronger and that of "neoantergan" was weaker. Of the last named, only one concentration (1·65%) has been tested. There are

substances with a strong antihistamine and almost no anaesthetic action, and others in which this relation is reversed. *H. Herxheimer*

2266. **Action of Histamine and of Synthetic Antihistamine Drugs on Capillary Permeability of the Blood-ocular Barrier.** (Action de l'histamine et des anti-histaminiques de synthèse sur la perméabilité capillaire de la barrière hémato-oculaire)
B. N. HALPERN, L. GUILLAUMAT, and S. CRUCHAUD. *Semaine des Hôpitaux de Paris* [*Sem. Hôp. Paris*] **24**, 2564–2565, Oct. 26, 1948. 7 refs.

The penetration into the aqueous humour of intravenously injected fluorescein was used to test the influence of histamine and of antihistamine substances on the capillary permeability in this region of the eye. Rabbits received 2 ml. of fluorescein; the time of the appearance of the fluorescein in the aqueous humour was observed by means of the slit lamp, while the intensity of the penetration was measured by the amperage of the slit lamp required for the observation. When 0·5 mg. per kilo of histamine dihydrochloride was injected together with the fluorescein the time of the appearance of the dye in the aqueous humour was not altered but the amount increased considerably, reaching a peak at about 8 minutes after injection. If 20 mg. per kilo of the antihistamine "3,277 R.P." ("phenergan") was given subcutaneously half an hour before, this action of histamine was not observed. *H. Herxheimer*

2267. **Effect of Phenylindanedione on the Prothrombin Level: I. Experimental Study on the Rabbit.** (Action de la phényl-indane-dione sur le taux de la prothrombine: I. Étude expérimentale sur le lapin)
J. P. SOULIER and J. GUÉGUEN. *Revue d'Hématologie* [*Rev. Hémat.*] **3**, 180–184, 1948. 2 figs., 3 refs.

2268. **Effect of Phenylindanedione on the Prothrombin Level: II. Clinical Studies.** (Action de la phényl-indane-dione sur le taux de la prothrombine: II. Utilisation de la P.I.D. en clinique humaine)
J. GUÉGUEN and J. P. SOULIER. *Revue d'Hématologie* [*Rev. Hémat.*] **3**, 185–195, 1948. 12 figs.

2-Phenylindanedione-1 : 3 (PID) depresses the prothrombin level in blood of rabbits. Doses of 10 to 20 mg. per kilo decrease the prothrombin concentration within 6 hours, to a minimum of 40% after 12–24 hours, while normal levels are regained in about 42 hours. Increase of dose to 40 to 80 mg. per kilo prolongs the effect, and depresses the prothrombin level to 20 to 30%. Toxic manifestations, consisting of renal damage, occur only with doses of 400 mg. per kilo.

PID was given post partum to 43 patients: 29 received a single dose of 10 or 20 mg. per kilo. Prothrombin minima between 15 and 52% were reached between the 30th and 54th hours, the normal level being recovered between the 60th and 100th hours. Synthetic vitamin-K analogues had no effect on the fall in prothrombin level, nor did they accelerate the return to normal. Repeated doses were given to 41 patients without incident, and 2 patients with femoral thrombosis received repeated doses every 3 days to keep the prothrombin level between 25 and 35%. Toxic manifestations were slight: polyuria and polydipsia, with dryness of the mouth and occasional slight tachycardia, were common; in 2 patients a scarlatiniform eruption developed, but faded within 5 days. Patients given PID excrete urine which is orange-coloured when alkaline but normal in appearance when acid; this is presumably due to the drug. *G. Discombe*

2269. **On a Possible Histamine Mechanism of Action of Some Drastic Purgatives.** (Sul possibile condizionamento istaminico dell'azione purgativa di alcuni drastici)
V. ERSPAMER and A. PAOLINI. *Archives Internationales de Pharmacodynamie et Thérapie* [*Arch. int. Pharmacodyn.*] **77**, 415–433, Nov. 1, 1948. 24 refs.

By administration of adequate doses of antihistaminic agents ("antergan", "antistin", "benadryl", "3015 R.P." and "3277 R.P.") it was possible to weaken, delay, or even abolish the action of various drastic purgatives (elaterium, castor oil, jalap resin, *Globularia alypum*) provoked in rats and cats. The more active product is 3277 R.P., the less active benadryl. The anti-drastic action of antihistaminic drugs does not seem to depend upon generic antispasmodic or anti-acetylcholinic properties, but rather upon specific "antihistaminic" properties. Histamine may perhaps condition the purgative action of the drastics studied. Histamine may, indeed, be involved: (*a*) directly in the capillary dilatation, in the increase of the capillary permeability, and in the irritation of the sensitive nerve endings of the intestinal mucosa (irritative stage of the drastic action); (*b*) indirectly, through nervous reflexes, in the dilatation of larger vessels and in the increase of secretions and of peristalsis (evacuating stage of the drastic action). Acetylcholine may be considered to condition the evacuative phase. [From the authors' summary.]

CHEMOTHERAPY

2270. **Effect of Chemotherapeutic Agents on *C. diphtheriae*, with Special Reference to the Diamidines**
L. F. HEWITT. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **29**, 447–452, Oct., 1948. 7 refs.

The author, working in the Medical Research Council Serum Research Institute in Carshalton, has examined the effects of sulphadiazine, sulphaguanidine, sulphamerazine, sulphathiazole, proguanil ("paludrine"), mepacrine, and the diamidines, propamidine, dibromopropamidine, hexamidine, and diiodohexamidine, as the soluble diisethionates, on *Corynebacterium diphtheriae*. Having shown (*Brit. J. exp. path.*, 1948, **29**, 181) that the lethal effect of *C. diphtheriae* is due to toxin formation and that antibacterial sera do not affect bacterial viability (*Brit. J. exp. Path.*, 1947, **28**, 338; *J. Path. Bact.*, 1947, **49**, 145), the author now describes part of a search for a chemotherapeutic agent effective against the organism.

Of the sulphonamides, sulphathiazole had a slight *in vitro* bacteriostatic effect at 50 μg. per ml., but the re-

mainder were inactive at 100 μg. per ml. Of the antimalarials, proguanil was bacteriostatic at 50 μg. per ml., in broth, and mepacrine slightly so at 2·4 μg. per ml., but the cultures were not sterilized rapidly. These compounds were not examined further. The diamidines, sterilized by steaming, were compared with streptomycin against a gravis Type I strain and the corresponding streptomycin-resistant variant. Diiodohexamidine was the most active at 0·3 μg. per ml. Cultures resistant to each of the diamidines were obtained by 11 to 17 serial subcultures in papain-digest broth. The resistance developed (5 to 10 times) did not differ for the ordinary and streptomycin-resistant strains, and resistance to one diamidine was not specific. Investigation of the toxin production showed that the development of resistance had not diminished the toxigenicity of the strains.

In protection experiments guinea-pigs weighing 250 g. were infected intracutaneously with 3×10^8 organisms in 0·2 ml. saline; 3 mg. of diamidine was injected subcutaneously 15 minutes before infecting, and 3 more 3 mg. doses were given at 2-hourly intervals, 2 guinea-pigs being used for each drug and for controls. Unlike streptomycin, the diamidines gave no protection. Local reactions, oedema and erythema (white-centred), to the drugs were obtained but there was no general disturbance.

Malcolm Woodbine

2271. **Chemotherapeutic Studies on a Series of Dithiocarbamates and their Bismuth Derivatives**

A. Goth and F. J. Robinson. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **93**, 430–433, Aug., 1948. 1 fig., 6 refs.

Since it has been found that the antibacterial activity of antibiotics of the aspergillic acid group was increased by the addition of bismuth, certain bismuth dithiocarbamates were studied. The dithiocarbamates, widely used as precipitants of metals, possessed antibacterial properties themselves, of an order of 0·2 to 5 mg. per 100 ml., against *Staphylococcus aureus* in broth. The bismuth dithiocarbamates were more potent, the minimal growth-inhibitory concentrations ranging from 0·02 to 1 mg. per 100 ml. The antibacterial spectrum of bismuth diethylthiocarbamate was wide; it was effective against *Brucella melitensis*, *Mycobacterium tuberculosis*, and *Bacterium coli* at a concentration of 0·1 mg. per 100 ml. It was also effective *in vivo* against an infection with Type I pneumococcus in mice.

R. Wien

2272. **Perirenal Hemorrhage in Ureter Ligated Dogs Receiving Phthalylsulfathiazole**

J. M. Little, S. L. Wallace, J. R. R. Bobb, and W. C. Crothers. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **66**, 338–341, Nov., 1947. 1 fig., 12 refs.

The ureters were ligated in 6 dogs, and phthalylsulphathiazole was administered orally in doses of 0·5 to 0·75 g. per kilo per day for 3 to 6 days before operation and continued after the operation until death supervened. At necropsy 2 of these dogs showed increased vascularity of the fascial sheath covering the perirenal fat, in 5 evidence of perirenal sheath haemorrhage was found, and 3 had fresh free blood in the abdominal cavity. In 4 out of 6 control dogs, in which the ureters were ligated but no drug was given, increased vascularity of the perirenal sheath was found at death, but none showed perirenal haemorrhage. The authors mention that in other experiments such haemorrhage did not occur when phthalylsulphathiazole was given to normal dogs, to dogs subjected to bilateral nephrectomy, or to dogs with ligated ureters in which the urine flow had become re-established. It therefore appears that administration of the drug and the presence of ureteric obstruction with intact kidneys are both necessary to produce the lesion; neither alone is sufficient. It appears also that the perirenal haemorrhage is due to vascular changes, since no abnormalities in prothrombin time, bleeding, clotting, and clot-retraction time, red blood cell counts, or platelet counts were demonstrated. The average total blood sulphathiazole concentration at the time of death in the test dogs was 2·9 mg. per 100 ml. The authors suggest that the clinical administration of phthalylsulphathiazole should be avoided in the presence of diminished renal function due to ureteric obstruction.

A. L. Walpole

PENICILLIN

2273. **Infection by Penicillin-Resistant Staphylococci**

M. Barber and M. Rozwadowska-Dowzenko. *Lancet* [*Lancet*] **2**, 641–644, Oct. 23, 1948. 17 refs.

This report deals with an extension of previous work by one of the authors; it is shown that the incidence of penicillin-resistant strains of *Staphylococcus pyogenes* giving rise to infection in the hospital in which the work was carried out is increasing.

All pus swabs received in the laboratory during the investigation were plated directly on to plain blood-agar plates and penicillin ditch-plates, the ditch containing 10 units of penicillin per ml. of agar. Only coagulase-positive staphylococci were included in the series. If any such organisms were shown on the ditch-plate to be resistant to penicillin, colonies (usually 10) were picked from a plain blood-agar plate and tested individually for penicillin resistance. Sensitivity to streptomycin also was tested on ditch-plates, the ditch containing 100 units of streptomycin per ml. of agar. Part of every ditch-plate was seeded with the Oxford staphylococcus as control. Specimens from 100 patients with staphylococcal infections were examined. From 59 patients penicillin-resistant strains of *Staph. pyogenes* were isolated; from 39 all colonies were resistant and from 20 both resistant and sensitive strains were isolated. Comparison with previous results showed that the incidence of patients yielding penicillin-resistant strains had risen from 14·1% in 1946 to 38% in 1947 and 59% in 1948. In view of claims that penicillin-resistant staphylococci can be rendered sensitive by growth in the presence of other organisms, whether the latter are sensitive or resistant to penicillin, the strains in this study were analysed according to their isolation in pure or in mixed culture. It was found that 34 of the 59 penicillin-resistant strains were originally isolated from 48 mixed

cultures, whereas only 25 penicillin-resistant strains were isolated from 52 pure cultures. All the 59 resistant strains produced penicillinase, and strains showing a minor degree of resistance were not encountered.

Streptomycin sensitivity was tested in 97 strains: 55 were penicillin-resistant, 13 were penicillin-sensitive strains isolated in association with 13 of the resistant cultures, and 29 were penicillin-sensitive strains isolated from cases yielding no penicillin-resistant colonies. All 42 penicillin-sensitive and 53 of the 55 penicillin-resistant strains showed a sensitivity to streptomycin similar to that of the Oxford staphylococcus.

It is considered that the widespread use of penicillin causes resistance in staphylococci in two ways: either a strain acquires resistance to penicillin or naturally resistant organisms, originally few, may survive while sensitive organisms are destroyed. In the present study it was found that, as regards penicillin-sensitive strains, 4 patients had had previous treatment with penicillin but 37 strains came from patients who had had no previous penicillin treatment. In the case of resistant strains, 29 came from cases with previous treatment and 30 from cases without such treatment. *R. B. Lucas*

2274. **Studies on the Depot Action of Oily Procaine-penicillin Suspensions.** (Untersuchungen über die Depotwirkung öliger Procainpenicillinsuspensionen)
A. F. Essellier, B. J. Koszewski, and F. O. Gundersen. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 1001–1004, Oct. 16, 1948. 6 figs., 8 refs.

The scope and limitations of penicillin therapy are fairly well recognized, and perhaps the most outstanding problem is a simplification of the method of administration of penicillin, on account of its rapid elimination and the need for frequent injections. Various means of retarding its action have been suggested, and Sullivan *et al.* (*Science*, 1948, **107**, 169) have described a procaine salt of penicillin which the present authors have employed in their work. Procaine penicillin is a crystalline compound consisting of equimolecular proportions of penicillin G and procaine. It is suspended in sesame oil so that 1 ml. contains 300,000 units of penicillin G and 124·5 mg. of procaine. Preliminary observations by Boger *et al.* (*Amer. J. med. Sci.*, 1948, **215**, 250) showed that in 50 patients no local pain or other reactions were encountered, and that 18 of 23 patients suffering from pneumonia recovered without complications after a single intramuscular injection of 300,000 units. The present authors found that after the single intramuscular injection of 300,000 units of procaine penicillin into 59 subjects, serum levels of over 0·03 unit per ml. were usually obtained. In 20 healthy persons (afebrile and with normal kidney function) the penicillin levels were maintained for a mean period of 30 hours (variation from 15 to 36 hours). Increasing the dose to 400,000 units did not further increase the duration of action (in 14 normal subjects), but 600,000 units caused a definite increase from a mean period of 30 to 48 hours (in 8 normal subjects). In 10 febrile patients an injection of 300,000 units produced a mean penicillin level of 0·03 unit per ml. for over 36 hours, corresponding to the effect produced by 600,000 units in afebrile patients. Similar results were obtained in afebrile patients suffering from renal deficiency, showing that in this condition the elimination of penicillin is obviously delayed. Penicillin was estimated by a haemolytic titration method and by the agar plate method. The clinical effects of procaine penicillin suspension were observed in 44 patients—18 cases of pneumonia (12 primary and 6 secondary), 11 cases of pyelocystitis, 3 cases of furunculosis, 2 cases of post-pneumonic pleural empyema, 3 cases of tonsillitis, 4 cases of erysipelas, 2 cases of subacute bacterial endocarditis, and 1 case of staphylococcal septicaemia. The patients with pneumonia received daily intramuscular injections of 300,000 to 600,000 units; the preparation was normally given for a further 2 to 3 days after lowering of the temperature. In empyema the same daily dose was given up to a total amount of 5,700,000 and 7,200,000 units. Two of the patients with erysipelas died, and at necropsy interstitial nephritis was evident, but this was considered to be in no way due to the action of procaine penicillin. The clinical effects were stated to be superior to those obtained with ordinary aqueous solutions of penicillin. It was concluded that the daily intramuscular injection of 300,000 units of procaine penicillin suspension produced a definite therapeutic response. In certain cases, such as those of subacute bacterial endocarditis, the dose should be increased to 600,000 to 900,000 units. The preparation was exceedingly well tolerated, the injections were painless, and no untoward reactions were observed, except for some eosinophilia and small, local, compact infiltrated areas, which only appeared some weeks after repeated injections. Experiments on guinea-pigs showed that small cystic areas were produced with some necrosis of the muscle fibres. *R. Wien*

2275. **The Absorption and Elimination of Caronamide (4′-Carboxyphenylmethanesulfonanilide)**
K. H. Beyer, E. K. Tillson, H. F. Russo, G. S. Schuchardt, and S. R. Gass. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **94**, 167–177, Oct., 1948. 3 figs., 23 refs.

The value of caronamide in delaying the excretion of penicillin has been established, but a precise study of the absorption and elimination of the compound has been delayed because of the need for a definite analytical method. The authors have used the colorimetric method of Ziegler and Sprague (*J. Lab. clin. Med.*, 1948, **33**, 96), which apparently determines total caronamide in body fluids, and the spectrophotometric method of Brodie *et al.* (*J. Pharmacol.*, 1947, **91**, 246). Although the latter gives lower caronamide values than the former, there is no assurance at present that it measures caronamide only to the exclusion of metabolites, and hence the results obtained have been designated as "caronamide *per se*". For their studies the authors used dogs. They found that caronamide was rapidly and almost completely absorbed by the oral route, maximal plasma concentrations being obtained within 30 minutes of its administration. At the same time the drug was also

rapidly excreted, some 43% of the dose appearing in the urine within 4 hours and practically the whole of it within 24 hours. None appears to be present in the faeces.

It was evident that metabolism of the compound took place rapidly and to a considerable extent, but the identity of the metabolite(s) is not known. About 60% of a dose appeared to be excreted as such, while the other 40% was excreted in the form of metabolite(s). The falling plasma concentrations of caronamide following intravenous administration were compared with those obtained with mannitol. It was found that the slope of the falling caronamide plasma-concentration curve was the same as, and that for its metabolite was less than, that for mannitol. The over-all elimination of caronamide (metabolism and excretion) was equivalent to the rate of elimination of mannitol. In dogs subjected to bilateral nephrectomy the volume distribution of caronamide appeared to be of the same order as that of mannitol. *G. F. Somers*

2276. **The Role of High Blood Penicillin Levels Achieved with Caronamide in Penetrating the Blood-Brain Barrier**
H. D. JANOWITZ, S. S. SCHNEIERSON, M. L. SUSSMAN, and F. H. KING. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 933–935, Aug., 1948. 8 refs.

In patients given caronamide in doses of 4 g. 3-hourly, injection of various doses of penicillin yielded high levels of penicillin in the blood, with concomitant high levels in the cerebrospinal fluid. In the absence of caronamide, the levels in blood and cerebrospinal fluid were far lower and far less persistent. It is suggested that caronamide might make intrathecal injection of penicillin unnecessary. *J. D. Judah*

2277. **Caronamide and Penicillin. Serum Levels in Human Beings, Following Multiple Doses of the Drugs**
M. MEADS, R. V. LONG, S. H. PACE, and G. T. HARRELL. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 874–877, Nov. 20, 1948. 3 figs., 11 refs.

The effect of caronamide given by mouth 4-hourly for 3 days on the serum penicillin levels of 17 patients was studied. None of them was over 60 years old or showed evidence of impaired renal, cardiac, or hepatic function, and all received 100,000 units of penicillin 4-hourly for 7 days. On the 2nd, 3rd, and 4th days caronamide was given 4-hourly, half an hour before meals. From 7 patients receiving 2 g., and from 5 receiving 4 g., 1 to 3 blood samples were taken 4 hours after administration of the drugs, and from 5 patients receiving 4 g. samples were taken after 2 hours. Serum was stored at −20° C. The penicillin content was estimated by a serial dilution method, and the caronamide by the colorimetric method of Ziegler and Sprague.

It was found that a concentration of 25 mg. of caronamide per 100 ml. of serum was necessary to achieve a twofold increase in penicillin concentration. A dose of 4 g. 4-hourly was required to produce a serum caronamide concentration of 30 mg. per 100 ml. 4 hours after administration. To obtain a fourfold or greater increase in penicillin content concentrations of caronamide exceeding this were required. The effect of the drug was cumulative, maximum penicillin levels being reached after 2 days. Nausea in 3 patients receiving 4 g. of caronamide was the only symptom of toxicity recorded. *J. E. M. Whitehead*

2278. **Penicillin Therapy with Prolonged Interval Dosage Schedules**
W. A. ALTEMEIER. *Annals of Surgery* [*Ann. Surg.*] **128**, 708–713, Oct., 1948. 7 figs.

The author cites the experimental work of others to show that in organisms temporarily exposed to penicillin there is a lag in growth after withdrawal of the antibiotic. This experimental work is confirmed and graphs are shown of the relative turbidity of strains of both haemolytic staphylococcus and streptococcus, with and without exposure for 2 to 4 hours to penicillin at a concentration of 2 units per ml. This lag in growth after withdrawal of penicillin is used as an argument against the need for maintaining a constantly high blood level in penicillin therapy and in favour of intermittent dosage at intervals longer than those previously thought desirable.

The main part of the paper consists in a review of the treatment of 161 common surgical infections with 100,000 units of penicillin every 8 hours, or 150,000 to 200,000 every 12 hours. Wherever possible the organism concerned was tested for sensitivity before beginning treatment. Levels in blood at hourly intervals were also determined in 68 cases after a single dose of 100,000 units, and wide variations were found. The cases treated are listed, and also the results of therapy by this modified scheme judged on clinical grounds. The author claims that, although this is a relatively small series of cases, the results compare very favourably with those to be anticipated from the more frequent injection of small doses. *C. Patrick Sames*

2279. **Fate and Distribution of Penicillin in the Body. II. Duration of Blood Concentration and Chemotherapeutic Effectiveness**
N. ERCOLI, M. N. LEWIS, B. S. SCHWARTZ, and M. WHITEHEAD. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 297–299, Nov., 1948. 14 refs.

The authors studied the relation between the duration of the therapeutic effect and the blood level of penicillin administered to albino rats weighing between 80 and 120 g. Potassium penicillin G in arachis oil containing 1 mg. per ml. of adrenaline was injected in doses proportional to weight. At various intervals the animals were bled and the blood levels determined by Rammelkamp's method. At corresponding intervals other groups of 10 to 20 rats were infected with 100 to 1,000 lethal doses of 18-hour broth cultures of either a Type 3 Group A streptococcus or a Type I pneumococcus. Most untreated animals died within 2 or 3 days; animals surviving 3 weeks were regarded as cured. In the pneumococcal infections there was evidence that the therapeutic effect outlasted the duration of the detectable

level of penicillin in the blood (0·015 to 0·03 unit per ml. serum). In the streptococcal infections, possibly owing to the heavy inocula used, the results were not so clearly defined, but there was evidence of a similar prolongation of therapeutic activity beyond the duration of the detectable level in the blood.

The authors discuss the interpretation of their studies in the light of other work on the relation of therapeutic effectiveness and penicillin dosage schedules.

J. E. M. Whitehead

STREPTOMYCIN

2280. **Streptomycin Treatment of Meningitis due to Gram-negative Saprophytes**

W. LEWIN and R. L. VOLLUM. *Lancet* [*Lancet*] **2**, 446–449, Sept. 18, 1948. 8 refs.

Five cases of meningitis are described, 3 of which occurred after surgical removal of a cerebral tumour or abscess and 2 after chronic ear infection. Inadequate dosage, developing resistance of the organism, an untreated primary focus, and pus formation are the causes of lack of response to streptomycin. It is therefore recommended that, when possible, treatment should begin with sulphadiazine pending estimation of the sensitivity. With an organism sensitive up to 10 units per ml. streptomycin should be injected intrathecally in daily doses of 50,000 to 100,000 units and the injections continued until the cerebrospinal fluid has been sterile for at least 5 days. Cerebrospinal-fluid streptomycin levels should be checked during treatment to ensure adequate dosage, as there may be considerable variation in the levels in the same patient after the same dose. It is important to start treatment before spinal block or frank pus has developed. No toxic effects of any kind were observed. In 3 cases—2 of *Pseudomonas aeruginosa* and 1 of *Bacterium coli* meningitis—the results were very satisfactory. In one case there was no improvement (*Proteus*) and in one (*Achromobacter*) a fatal result, the former being associated with relative insensitivity of the organism, and the latter with rapidly developing resistance while apparently adequate doses were being received. *A. M. Stewart-Wallace*

2281. **Stomatitis due to Streptomycin. Report of Three Cases**

H. BEHAM and H. PERR. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 495–496, Oct. 16, 1948. 1 fig., 8 refs.

Three cases are reported of patients suffering from tuberculosis who during treatment with streptomycin developed painful stomatitis, which disappeared when the treatment was stopped. Two of the patients had pulmonary tuberculosis; in the third the disease first affected the upper vertebrae, and this led to an abscess involving the fifth to seventh dorsal vertebrae and eventually to acid-fast infection of the lungs. Streptomycin was given in doses of either 1 or 2 g. daily, and in the three cases the stomatitis developed 4, 5, and 12 weeks respectively after treatment was started. The clinical picture in the 3 cases was the same: a painful erosive membranous stomatitis which involved all the mucous membrane of the mouth as well as the under surface of the tongue. Treatment with gargles of warm saline and painting with 1% brilliant green did not prevent the vesicles from eroding, but as soon as streptomycin was stopped an improvement took place, and the lesions disappeared within a fortnight. When treatment was started again a similar rash broke out. There were no other toxic reactions, except for a mild cutaneous eruption in 2 cases. *T. E. C. Early*

2282. **Streptomycin in Topical Therapy. I. Its Sensitizing Property**

L. GOLDMAN and M. D. FELDMAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 640–641, Oct. 30, 1948. 9 refs.

The authors examined 212 patients for sensitivity to streptomycin by a patch test in which an ointment containing 5,000 units of streptomycin per gramme of cream base was used. None was positive, nor were any of 129 re-tested after two weeks. In contact tests performed with streptomycin powder on the buccal mucosa, and with the ointment on the vaginal mucosa, in 26 and 25 patients respectively, there were no positive reactions. Attempts at facial sensitization with the ointment in 17 patients also failed. In 300 cases of superficial pyogenic infections of the skin treated with streptomycin ointment, sensitization was clinically manifest in 3 patients, and these were found to have a positive reaction to the patch test. *J. E. M. Whitehead*

OTHER ANTIBIOTICS

2283. **The Antibacterial Action of Some Antibiotics, Studied with the Electron Microscope.** (L'azione antibatterica di alcuni antibiotici, studiata col microscopio elettronico)

B. BABUDIERI. *Rendiconti Istituto Superiore di Sanità* [*R.C. Ist. sup. San.*] **11**, 577–598, 1948. 39 figs.

It is generally accepted that penicillin and most of the other antibiotics have a double action. They are bacteriostatic in relatively low concentrations and bactericidal in higher concentrations. The author studied these phenomena with the electron microscope, in the Department of Hygiene of the University of Rome. Organisms used for this purpose included the Oxford *Staphylococcus aureus*, *Salmonella typhi*, *Bacterium coli*, *Bacillus anthracis*, *B. subtilis*, *B. rhinoscleromatis*, *Brucella melitensis*, *Proteus*, dysentery bacilli, and free-living leptospira. The antibiotics used were penicillin, streptomycin, streptothricin, expansin, and subtilin. Specimens were fixed with osmic acid. Morphological changes induced by sub-inhibitory doses of antibiotics and by massive doses were observed. Broth cultures re-inoculated in broth four times at intervals of 12 hours were exposed to a partially bacteriostatic concentration of the antibiotic.

Penicillin first caused considerable increase in the length of bacilli, and the membrane became more

obvious. Later the membrane separated along the whole bacterium, as if the protoplasm had retracted. This was not observed with staphylococci. In the next stage, the length of the bacilli still increased, the protoplasm mostly remaining opaque and occasionally being vacuolated. Cocci increased in size. The transverse diameter of bacilli at first increased only to a limited extent, but later the whole body became enormously swollen and patchy, the membrane being invisible and the protoplasm translucent in an irregular way.

In bactericidal concentrations of the antibiotics lysis occurred, this taking place first in those organisms which had reached the stage of considerable swelling. Lysis always started from the centre of the protoplasm which became increasingly translucent, but not at the poles. Clearing of the protoplasm was sometimes patchy. At the end of lysis an empty membrane remains with an occasional opaque patch of protoplasm. In a culture of severely affected organisms there are always a few which are not affected or are only slightly changed. The different stages of lysis are similar in most sensitive organisms. Penicillin causes swelling and a marked loss of translucency in spores of *B. subtilis*. Inside the spore is a transparent structure containing numerous opaque granules. There are, however, spores which remain unchanged. The effect of other antibiotics on different organisms appears to be very similar, as regards the electron microscopical picture. The author objects to the view that the action of streptomycin consists in causing early senility of bacteria. According to the author the antibiotics arrest the reproductive property of the bacteria suddenly but their assimilative capacity is conserved, hence the frequent occurrence of giant forms, while ageing results in a concurrent loss of both reproductive and assimilative power. The paper is illustrated with 39 photomicrographs demonstrating the changes observed through the electron microscope.

E. Forrai

2284. **An Antibiotic from *Bacillus mesentericus***

J. MILLER and D. ROWLEY. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **29**, 452–457, Oct., 1948. 9 refs.

The authors, working in the laboratories of the Wright–Fleming Institute of Microbiology, St. Mary's Hospital, isolated an organism by Waksman's crowded-plate method. It was identified as *Bacillus mesentericus* and found to inhibit a range of pathogens, including *Staphylococcus aureus*, *Staph. albus*, *Corynebacterium diphtheriae*, *Streptococcus viridans*, *Bacillus anthracis*, *Klebsiella pneumoniae* and *Salmonella typhi*, on agar and in the presence of blood. *Bact. coli* and *Pseudomonas pyocyanea* were not inhibited. Growth in a casein-hydrolysate medium with added growth factors and maltose gave the best results. The antibiotic was assayed by a broth dilution technique with *C. diphtheriae* as test organism, but the agar cup method could be used for non-sterile solutions. Subcultures of the broth dilutions on to agar plates were made to assess the bactericidal effects. As Seitz filtration absorbed most of the activity, the pellicle was filtered off through muslin and the filtrate sterilized by using an 0·9 μ. gradocol membrane. Activity was lost by heating to 100° C. for 10 minutes at *p*H 6·5 and, after 24 hours at 20° C., the greater part of the activity had disappeared. At *p*H 2·0, the antibiotic could be extracted with ether, chloroform, and ethyl acetate. Chromatographic adsorption on activated alumina gave 5 distinguishable coloured bands. On elution with 0·2M phosphate buffer, the activity was found mostly in the brown band. Analysis of the brown solid eventually obtained (512 units per mg.) gave 49·35% C, 6·06% H, and 6·00% N with an approximate molecular weight of 180, assuming the antibiotic to be a monobasic acid. The antibiotic was 10 times more toxic to *Staph. aureus* than to leucocytes by the slide cell technique and was not similar to any other antibiotic. The instability, difficulties in handling the volumes of media required, and the not very promising chemotherapeutic properties led to the abandoning of further work.

Malcolm Woodbine

2285. **The Chemical Nature of "Cassic Acid": Its Identification as Rhein**

M. ANSCHEL. *Bulletin of the Torrey Botanical Club* [*Bull. Torrey bot. Club*] **75**, 580, 1948. 7 refs.

The isolation of an antibiotic, "cassic acid", from the leaves of *Cassia reticulata* Willd was reported in 1947 by Robbins, Kavanagh, and Thayer (*Bull. Torrey bot. Club.*, 1947, **74**, 287). "Cassic acid" is an anthraquinone derivative with two hydroxyl groups and one carboxyl group. The properties of this substance were so similar to those of a substance originally isolated from rhubarb by Hesse in 1895 that it seemed possible that they were identical. Studies of the antibiotic from *Cassia reticulata* and of rhein from *Rheum officinale* and from *Cassia augustifolia* show that they are identical both chemically and antibiotically. The structure of rhein is 4: 5-dihydroxyanthraquinone 2-carboxylic acid.

G. M. Findlay

2286. **Antibiotic-producing Organisms in Faeces and Sewage**

T. L. SU. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **29**, 466–473, Oct., 1948. 15 refs.

In the Sir William Dunn School of Pathology, Oxford, some 448 strains of bacteria, isolated from a variety of faeces and from samples collected from an Oxford sewage plant, were examined in an attempt to obtain new antibiotics. The author refers to the belief that the short survival of pathogenic organisms in soil and sewage might be due to microbial interaction. It was hoped that this work might throw some light on the part played by antibiotic formation in such cases. The species studied included, in order of frequency, the Gram-negative intestinal bacilli, *Streptococcus*, Gram-positive aerobic spore-forming rods, *Achromobacterium*, *Micrococcus*, *Chromobacterium*, *Staphylococcus*, *Proteus*, *Lactobacillus*, *Bact. faecalis alkaligenes*, *Clostridium*, and *Zooglea*. Pure cultures of the isolated bacteria were tested by the streak method against one strain each of *Staph. aureus*, *Bact. coli*, *Salmonella enteritidis*, *Pseudomonas pyocyanea*,

and *Corynebacterium xerosis*. Of the 448 organisms isolated, 74 (16.5%) inhibited growth of one or more of these test organisms. The percentage of active strains isolated was practically the same from faeces as from sewage. More than half the Gram-positive aerobic spore-forming rods and 9% of the Gram-negative intestinal bacilli were active and 2 of the 22 micrococci and 3 of the 19 staphylococci were also active. None of the 98 strains of streptococci was active, nor were the strains of *Proteus*, *Clostridium*, and *Zooglea*. Of the active strains, 70% inhibited the Gram-positive test organisms and 20% both the Gram-positive and Gram-negative organisms; the Gram-negative intestinal bacilli tended to inhibit only the Gram-negative test organisms.

Malcolm Woodbine

2287. **Micrococcin. An Antibacterial Substance Formed by a Strain of *Micrococcus***
T. L. Su. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **29**, 473–481, Oct., 1948. 1 fig., 5 refs.

During the search for antibiotic-forming bacteria in faeces and sewage the author, working in the Sir William Dunn School of Pathology, Oxford, isolated a strain of *Micrococcus* which was inhibitory to Gram-positive organisms, including *Mycobacterium tuberculosis*, but inactive against Gram-negative organisms. The organism is a facultative anaerobe, Gram-positive, non-motile, of diameter 0·7 to 1·4 μ., oval in shape and occurring in pairs, tetrads, or short chains, in clusters or singly. It grows well on ordinary nutrient agar at 37° C. to give faintly greyish circular colonies, 1 to 2·5 mm. in diameter, with entire edges and a finely granular shining surface. No liquefaction is produced in gelatin, blood is not haemolysed, and plasma is not coagulated. Glucose, maltose, and sucrose are fermented with formation of gas; litmus milk is turned slightly alkaline but without a clot being formed. Hydrogen sulphide and indole are not produced and nitrates are reduced to nitrites but methylene blue is not reduced.

Micrococcin is assayed by dispensing 1 ml. quantities of double strength agar, adding equal volumes of the sample serially diluted in water to the tubes of agar, plugging with absorbent cotton wool, autoclaving for 20 minutes at 0·5 atmospheres, mixing, and allowing to cool. The surface of the agar is then inoculated with a spore suspension of *Bacillus subtilis* and the excess inoculum drained off by inverting the tube in a large test-tube, where it is left during incubation. Results are read after overnight incubation at 370° C. The end-point is clear, the presence of occasional resistant variants does not vitiate the test, and sterility is not absolutely necessary. Media containing meat extract and peptone gave the best yields of the antibiotic at *p*H 7·4, with aeration for larger quantities. After incubation for 3 days, when the *p*H reaches 8·4 to 8·6, micrococcin could be extracted by: (1) acid precipitation (HCl), (2) charcoal adsorption or, less satisfactorily, (3) chloroform extraction.

Micrococcin so produced is an odourless, tasteless, amorphous cream powder, soluble in alcohol, acetone, chloroform, propylene glycol, glacial acetic acid, and pyridine and insoluble in ether, benzene, amyl acetate, glycerin, and vegetable oils. It is slightly soluble in hot water and has not been obtained crystalline. Micrococcin is dialysable, of melting point 220° to 223° C., loses little activity on heating to 230° C. for 5 minutes, keeps for over a year in the refrigerator, and is dextrorotatory. Micrococcin gives a blue fluorescence in the ultraviolet range with a peak at 345 mμ. The molecule contains N and S but no halogens and gives a negative ninhydrin reaction. The antibacterial effects are not reduced by incubating with pepsin or trypsin or by horse blood or serum, but inoculum size has some effect on the end-point. Micrococcin is mainly bacteriostatic and no signs of lysis, morphological changes, or alteration in staining character occur in susceptible bacteria. Micrococcin is active only against Gram-positive organisms. Resistant strains are easily produced and, once obtained, appear to be permanent. Micrococcin is inactivated or removed when added to a culture of a resistant staphylococcus in broth. The activity can be restored by heating for 3 minutes at 100° C. and by extraction of the antibiotic in chloroform. No cross-resistance between micrococcin and penicillin could be found.

Malcolm Woodbine

TOXICOLOGY

2288. **Therapy of Acute Fluoride Poisoning**
J. H. Peters. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 278–285, Sept., 1948. 54 refs.

The author describes a case of acute fluoride poisoning and discusses the treatment, concerning which very little has so far been written.

A girl aged 16 deliberately took between 50 and 80 g. of sodium fluoride; this is the largest recorded non-fatal dose. She had severe abdominal cramps, copious vomiting, and watery diarrhoea. Fragments of mucosa, presumably gastric, were found in the vomit. This vomit caused erythema and slight induration of the skin, which persisted for 7 hours. Salivation was profuse and the abdomen very tender. Her temperature rose to 102° F. (38·9° C.). The stomach was washed out and then lime-water was given by mouth, 1 oz. (28·4 ml.) every 30 minutes for 12 hours. Intravenous glucose saline and whole blood were administered to combat salt loss and shock. Early signs of tetany developed and were promptly relieved by calcium gluconate. Steady improvement followed, being almost complete in 3 days. The patient was discharged in 7 days. The urine was normal save for glycosuria due to the intravenous glucose.

The author discusses the chemistry of acute fluoride poisoning. Tetany is attributed partly to vomiting and partly to precipitation of serum calcium by fluoride. Oral calcium precipitates unabsorbed fluoride, and parenteral calcium replaces that precipitated by absorbed fluoride. Deaths have occurred with doses of 4 to 5 g., and success in the present case after at least ten times this amount is attributed largely to prompt treatment with

calcium orally and parenterally. Tetany can rapidly progress to death in this condition. A high volume of urine should be maintained by adequate parenteral fluids. *C. L. Cope*

2289. **A Case of Fluid Xylol Poisoning.** (Zatrucie płynnym ksylolem)
E. RUŻYŁŁO. *Polski Tygodnik Lekarski* [*Polsk. Tyg. lek.*] 3, 949–952, Aug. 2–9, 1948. 9 refs.

The author describes a very rare case of acute poisoning due to fluid xylol, and reviews the relevant literature on the better known chronic poisoning from xylol fumes, mainly encountered among printers.

A man aged 25, for suicidal purposes, drank half a glass of xylol. Severe burning pains in the mouth, retrosternally, and in the epigastrium were experienced immediately afterwards, followed by slight dyspnoea and rapid swelling of lips and tongue. A stomach washout 45 minutes later resulted in distinct relief; consciousness was clouded, but the patient complained of severe pain in the whole abdomen and oesophagus. Mucous membranes were bright red, dry, fissured, and tender. The pulse was weak; the pupils were dilated, reacting sluggishly, and the tendon reflexes accentuated. Seven hours after the onset blood examination revealed traces of xylol. The patient was conscious but apathetic, complaining of burning pain in the epigastrium, headache, generalized weakness, and indistinct vision. Apart from lower facial nerve weakness, there were no neurological signs. There was oliguria, with increased urobilinogen in the urine. Light diet was well tolerated. On the next night the patient was sleepless and excited. On the second day he felt weak; headache was worse but eyesight good. There was blood in stools (after an enema). On the third day the symptoms persisted. There was a haemoglobin value of 72% and an erythrocyte count of 3,940,000 per c.mm. A barium meal examination gave negative results. During the next 3 days symptoms gradually retrogressed completely.
H. Maslowski

2290. **Methyl Bromide Poisoning.** (Les intoxications par le bromure de méthyle)
H. ROGER and R. SIMONIN. *Annales de Médecine* [*Ann. Méd.*] **49**, 486–498, 1948.

After a brief historical survey, the authors give a full clinical description of methyl bromide poisoning. In mild cases there is vertigo, drowsiness, and headache, with return to normal within a few days. In cases of average intensity, the above symptoms are more severe and there may be tremor and myoclonic jerks. There is marked asthenia, and painful hyperacusis and transient blindness occasionally occur. All these symptoms take some 3 months to clear up. In severe poisoning, symptoms appear either immediately or after a latent period of 2 to 3 hours. Death may occur within 48 hours in status epilepticus. In other cases the patient recovers from coma but continues to have generalized or localized fits. A peculiar tremor develops, usually unilateral and affecting mainly the arms. There may be other signs of extrapyramidal involvement. All these disturbances are permanent. Less conspicuous are mental changes, signs of cerebello-labyrinthine involvement, and visual disturbances. The authors discuss the pathology of the condition. They believe that the condition may be accounted for by a vasomotor crisis leading to more or less permanent lesions. A brief note is given on prophylaxis and treatment. *J. F. Delafresnaye*

2291. **The Effect of 2,3-Dithiopropanol (BAL) on Gold Toxicity in Rats**
C. S. GILLMOR and R. H. FREYBERG. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1024–1028, Aug., 1948. 6 refs.

The influence of 2 : 3-dimercaptopropanol (BAL) on gold toxicity in rats was investigated. It appears that BAL protects rats from gold poisoning only when it is administered simultaneously with the gold; when injected 3 days after the gold it had no effect on the course of poisoning. [No data are included in this report which indicate the mode of the protection.] *J. D. Judah*

INDUSTRIAL TOXICOLOGY

2292. **Study of Punctate Basophilia in the Accumulator Industry.** (Étude de la granulobasophilie hématique dans l'industrie des accumulateurs)
M. DUVOIR, L. DEROBERT, and A. HADENGUE. *Archives des Maladies Professionnelles* [*Arch. Mal. prof.*] **9**, 365–377, 1948. 16 figs., 5 refs.

A research laboratory in a French accumulator factory carried out investigations to determine the processes involving most risk. It was noted that some production of lead dust occurred in the foundry when plates were being trimmed and that greater risks were present in the process of coating these, especially if this was done by hand rather than by machine. Material shortages made it necessary to recover used plates, a particularly dangerous procedure.

Among 50 workers 38 never had punctate basophilia. These men worked in the foundry; the other 12 had slight and transient changes. Six of the 50 men had moderate anaemia, the red cell count lying between 3 and 4 million per c.mm. In the kneading shops from 3 to 5 men worked. The great danger of this process was countered if the men worked in it for 3 weeks alternately with 3 weeks in a completely safe employment. Masks were worn and the whole shop was kept damp. Blood examinations were made every 2 months. Three-fifths of the men had fairly constant basophil changes. In the coating and assembly shops 13 out of 38 men never had pathological blood changes; 12 had transient and 13 permanent variations from normal. The personnel working on the recovery of old batteries was frequently changed so that only 15 men could be examined at frequent intervals; 40% had permanent basophilia. Some sweepers and cleaners also had blood changes. These persons took no precautions at all and were variously employed.

Basophilia generally develops, if at all, in the first or

second month of employment. In 1 case it was noted after 8 days. It appears desirable to cease exposure of any men with more than 0·5 basophilic cells per field, but economic necessity made it unavoidable to employ some men after the basophilia had reached a theoretically dangerous level. One man having a figure of 0·50 per field had 80 μg. per litre of lead in the blood, 80 μg. in the urine, and coproporphyrinuria of 600 μg. When the basophil cell count rose to 1·10 per field the subject was given tricalcium phosphate and vitamin D. During a treatment lasting for 40 days the count of abnormal cells gradually fell to 0·50. A gradual deterioration of the blood condition in the next 3 weeks led to removal of the workman from further exposure. Basophilia rapidly diminishes when the workman is removed from any lead hazard and generally disappears in 2 or 3 months but may persist in moderate form for a year. It was not possible to determine the relation between the degree of basophilia and the level of lead in the blood.

G. C Pether

2293. **Possibility of Replacement of Aromatic Hydrocarbons by Less Toxic Products.** (Possibilités de remplacement des hydrocarbures benzéniques par des produits moins nocifs)
P. LAFARGE. *Archives des Maladies Professionnelles* [*Arch. Mal. prof.*] **9**, 378–387, 1948.

The war caused a relaxation of precautions with volatile solvents, so that poisoning by benzene and other harmful materials became more frequent in France. A commission was recently appointed to discover safer substitutes for some of the aromatic hydrocarbons. In the rubber industries benzene solutions have advantages over others and can be replaced only by trichlorethylene or certain special petroleum solvents. In the waterproof clothing trade poisoning and fatalities from the use of solvents are frequent. Some adhesives with a trichlorethylene solvent are extremely useful, but the odour is unpleasant though there is no fire hazard. Petrol is useful but is most effective because of the presence of benzene compounds which may amount to 10%. In the shoe industry petrol is preferred to benzene or trichlorethylene. In the flower and feather trade attempts are being made to introduce adhesives with a latex base, and water glues containing suspensions of vinyl resins have been tried. Spirits of turpentine are used to dissolve paints and varnishes but tetraline and decaline are also employed or white spirit. The last contains some higher homologues of benzene. Benzene itself is not used. The cellulose lacquers are dissolved in ethyl, butyl, or amyl acetate; they do not dissolve in the benzene hydrocarbons. A return is gradually being made to toluene or xylene which are preferable to benzene. The alcohols are theoretically useful but are too dear and difficult to obtain. Synthetic paints and varnishes which are essentially formaldehyde phenolic resins or glycerophthalic resins may be dissolved in benzene or heavy naphtha. Bituminous varnishes and those used for mirrors may be dissolved in petrol solvents. Coal by-products must be dissolved in naphtha or in coal spirit. Dammar gum is the base for varnishes used to protect mirrors, and gilsonite or bitumen is also used in this way. It would seem desirable to replace benzene by toluene for solvent purposes. Inks for heliogravure can conveniently be dissolved in trichlorethylene rather than in benzene, and poisoning from the latter is not uncommon in printing works. Solvent naphtha or white spirit could also be used with advantage. Imitation leathers are made by covering a basal fabric with a cellulose. Rapid drying is essential and mixtures of methyl and ethyl acetate with benzene are used as solvents. Poisoning from the benzene is rare; toluene is not considered a good substitute for technical reasons. Benzene is by no means essential for the extraction of oils and fats and may be harmful to materials and to colours. Bones and various seeds may be extracted with trichlorethylene, with crude petroleum, or with benzene. As the processes are closed ones no special precautions are needed. Trichlorethylene may also be used to clean grease from metals. For dry cleaning solvent naphtha, trichlorethylene, and benzene are used. The evolution of fume is intermittent and poisoning is not common. Solvent recovery is practised in the larger works. It is concluded that no general prohibition of the benzene hydrocarbons is possible. Trichlorethylene has many advantages though some workers dislike it despite medical recommendation. The petroleum solvents are generally complex substances and successive samples of the supposedly same substance are found, on examination, to vary considerably. It would seem desirable to make exclusive use of the Venezuela oils for cleansing purposes since these contain low percentages of aromatic compounds. In many cases light solvent naphthas could easily be substituted for benzene. Benzene should be forbidden and both toluenes and xylenes should be defined and their use controlled.

G. C. Pether

2294. **Industrial Poisoning with Nitrogen Mustard.** (Gewerbliche Vergiftungen durch ***beta-beta***-Dichlordiäthylmethylamin (Stickstoff-Yperit, Nitrogen Mustard))
A. JORDI. *Helvetica Medica Acta* [*Helv. med. Acta*] **15**, 470–473, Nov., 1948.

The author describes 7 cases of poisoning by nitrogen mustard, which is used in the preparation of pethidine (dolantin). This substance boils at 70° C. and is slightly volatile. The lesions caused thereby are almost identical with those which develop from exposure to the sulphur analogue. Blisters developed a little more slowly than with the latter substance, in one case after 8 days' interval. The connective tissue round the eyes and the upper respiratory tract was readily affected by nitrogen mustard and hoarseness was often prolonged. In one patient a toxic pneumonia developed.

Nitrogen mustard is particularly damaging because of its effects on enzymes and seems to affect many, both *in vivo* and *in vitro*. It is therefore not surprising that a toxic action on the liver was most evident. Increased urobilinogen appeared early in the urine and of the 5 patients investigated every one had hepatic involvement. Bilirubin was sometimes increased in the blood, with a positive Takata-Ara reaction. One patient was exposed to risk for a year but continued at work for this period.

When he stopped work, results of the galactose test gradually returned to normal. The patient who had a toxic pneumonia showed simultaneous evidence of liver damage, but the results of the tests became more nearly normal as his condition improved. Later he had a mustard burn of the hand and a month afterwards the galactose test was strongly positive. General lassitude was a common symptom in those who had been poisoned. Changes of pigmentation were seen similar to those occurring with mustard gas. Some patients had a yellowish coloration of the conjunctiva, others had urticarial spots, oedema of the lips, or night blindness. In the skin and mucous membranes an allergic state develops to the irritant as with mustard gas. Bronchial asthma may develop after prolonged inhalation of α, β-dichlorodiethyl ether, but in contrast α,α′-dichloroethyl ether exerts only a general toxic effect.

The blisters caused by nitrogen mustard were treated by application of 1 in 3,000 silver nitrate, the chlorine ion being rapidly fixed by the silver. Cod-liver oil ointment has also been useful in treating wounds and conjunctivitis. The general intoxication may be partly remedied by injections of vitamins including C and B_1. Injections of a calcium preparation appeared to benefit the respiratory symptoms, and the unsightly pigmentations of the skin responded to the application of 10% salol in petroleum jelly.

Prophylaxis is most important, and the author does not think that nitrogen mustard has such a selective action as to be free from risk when used therapeutically. Although the workers examined were in fact exposed very little, it appears that more severe contamination would have caused permanent damage. Nitrogen mustard should be listed as a toxic substance so that victims of industrial poisoning may be compensated. Severe blood changes were not observed. *G. C. Pether*

2295. **Toxicological Studies on Certain Commercial Silicones and Hydrolyzable Silane Intermediates**
V. K. Rowe, H. C. Spencer, and S. L. Bass. *Journal of Industrial Hygiene and Toxicology* [*J. industr. Hyg.*] **30**, 332–352, Nov., 1948. 2 figs., 9 refs.

The term " silicone " describes the organosilicon oxide polymers as a class. These substances are produced in a wide variety of physical forms, including fluids, resins, and rubber-like products. They are of increasing industrial importance, but little if any information is available regarding their toxicological properties, and this paper deals with the action of some of the principal silicones on laboratory animals. Silicones may be regarded as organic derivatives of silica, SiO_2, wherein some of the oxygen of the polymers is replaced by organic groups.

The chlorosilanes investigated are colourless liquids which react violently with water to form HCl and polysiloxane condensation products. A single dose of the substance was given—as a 10% solution in light mineral oil—by a stomach tube to rats. The rats were kept under observation for a fortnight, and 0·1 or 0·3 g. per kilo of the following substances—$C_2H_2Cl_2Si$, $C_4H_{10}Cl_2Si$, CH_3Cl_3Si, and $C_2H_5Cl_2Si$—did not prove fatal in this period, but 1 g. per kilo almost always did so, owing largely to its corrosive action. When administered intraperitoneally the action of the substances was at least ten times more powerful. When applied to the shaven skin of rabbits they caused severe corrosion in 1 to 3 minutes. The introduction of a small drop (about 0·05 ml.) into the eye of rabbits resulted in severe damage, so it is evident that when human beings handle these substances the utmost care must be taken to prevent all bodily contact. A single exposure of rats to the vapours of $SiCl_4$ and $(C_2H_5)SiCl_2$ for 5 to 15 minutes caused eye and nose irritation, salivation, and shallow breathing.

The ethoxysilanes investigated are liquids which are oil-soluble, and slowly decompose water so as to form alcohol and polysiloxane condensation products. They were administered by stomach tube to rats, and a dose of 0·6 or 1 g. per kilo was usually not fatal. A dose of 1·4 to 7 g. per kilo was usually fatal in a few hours, but the results were rather erratic. Quantities of the substances ranging up to 0·2 ml., when dropped into the eye of a rabbit, caused immediate marked irritation, but the effect was transitory and the eyes were normal after 24 hours. The substances caused no appreciable irritation when applied to the skin of rabbits. When rats were given a single exposure to a concentration of 1,000 to 4,000 parts per million (p.p.m.) of the vapour for a period of 1 to 8 hours the effects of the different substances varied greatly. For instance, diethoxydimethyl silane $(CH_3)_2Si(OC_2H_5)_2$, caused no mortality, while tetraethoxysilane $(C_2H_5O)_4Si$), if breathed for more than 3 hours, was almost always fatal. The effects of repeated exposures to smaller concentrations of the two silanes mentioned supported the results obtained with single doses. A concentration of 500 p.p.m. of the poisonous tetraethoxysilane was administered for three to five 7-hour exposures to 10 rats, with fatal results. A dose of 250 p.p.m. caused the rats to lose weight slowly until they died or were killed. They suffered pronounced renal damage, but no other pathological changes were observed. In the tests with 125 p.p.m. of the silane the rats were exposed on 5 to 30 occasions, and they showed a gain in weight throughout. They were normal in appearance, though there was some damage to the kidneys. In the tests with diethoxydimethyl silane, concentrations of 500 to 2,000 p.p.m. of the vapour had no effect, but when 10 rats were exposed to 4,000 p.p.m. for ten 7-hour periods, 7 survived, though with a loss of weight, while the animals killed showed acute lung involvement.

The silicones of organopolysiloxanes are insoluble in water and alcohol, are non-volatile and non-crystalline, and are good dielectrics. A huge number of different fluids and resins can be made by varying the hydrocarbon groups attached to the silicon atoms. The most important liquid silicones are those in which the organic radicals are all methyl, or methyl and phenyl. These fluids are used as, among other things, high- and low-temperature lubricating oils. The methyl polysiloxane fluids are manufactured in an almost continuous series of molecular sizes from hexamethyldisiloxane to polymers in which the $-Si(CH_3)_2-O$ groups number 1,000 or more.

Single oral doses of 7 members of the series were given to guinea-pigs by stomach tube, and the animals were kept under observation for the subsequent week. The toxicity of the fluids was found to be very low, the response induced being similar to that caused by ordinary mineral oil. When repeated doses were given by stomach tube to rats, they continued to grow well even at the highest dosage level, while the blood and tissues in general showed no changes. When single or repeated intraperitoneal injections were made in rats the reaction was typically that of a non-irritating foreign body, except for hexamethyldisiloxane, which caused widespread irritation. Similar results were obtained when the silicones were injected intradermally. When they were dropped into the eyes of rabbits some of them produced transitory irritation, but the eyes were normal again 24 to 48 hours later. Exposures of rats and guinea-pigs to the vapour of hexamethyldisiloxane caused little if any effect unless the air was saturated with the substance.

The silicone compounds studied were methyl or methylphenylpolysiloxanes containing various fillers. The possible number of such substances is great, and two were selected for study. One of them had a consistency like petrolatum, and the other was of a grease-like character. Their oral administration had no effect on the growth and appearance of rats, but they caused transient irritation when instilled into the eyes of rabbits. The silicone resins studied were methyl or methylphenyl bodies of high molecular weight in which there was molecular cross-linking. These products are used as insulating varnishes and heat-resistant protective coatings. They had little if any influence on the rate of growth of rats or on the microscopical appearance of the tissues.

H. M. Vernon

See also Section Medicine: General, Abstract 2409.

INSECTICIDES

2296. **DDT [2,2 Bis (*p*-Chlorophenyl) 1,1,1-Trichlorethane] Poisoning. Histopathologic Observations on the Central Nervous System in So-treated Monkeys, Dogs, Cats and Rats**

J. H. Globus. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] 7, 418–431, Oct., 1948. 6 figs., 17 refs.

A general review of the literature on the toxicity of DDT in animals and man is given. Experiments were carried out with 3 monkeys, 4 dogs, 5 cats, and 6 rats, to which DDT was administered under varying conditions and for different periods of time; although the majority of the animals so treated showed signs of DDT poisoning and although some of them apparently died as a result of administration of the drug, no morphological alterations were found in the brain and spinal cord which could be regarded as due to the DDT. There was no increase in free fat or glial elements, including compound granular cells and microglia. Small differences in staining were as common in the controls. It is concluded (though the dosage employed in some of the experiments may have been too low) that the results do not explain the symptoms, and it is suggested that these may be produced by a selective action on the neurones without the production of morphological changes.

W. E. Kershaw

2297. **Toxicological and Pharmacological Studies on the Powdered Stem of *Ryania speciosa*, a Plant Insecticide**

S. Kuna and R. E. Heal. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] 93, 407–413, Aug., 1948. 10 refs.

The insecticide was obtained from the ground stem of the tropical plant *Ryania speciosa* Vahl, and used as the undiluted powder or as a dust mixed with talc and containing 5% rotenone. It is effective against the cornboring *Pyrausta nubilalis*, the Oriental fruit-moth, and several other species of insects of economic importance. The acute oral toxic dose was determined in mice, guinea-pigs, rabbits, chickens, dogs, and monkeys, and ranged from 150 mg. per kilo in dogs to over 3,000 mg. per kilo in chickens. It was about four times more toxic than DDT in mice in acute toxicity experiments, but considerably less toxic from a cumulative point of view. During a 5-month period the concentrations tolerated in the diet by various animals were 1% of *Ryania* powder, 0·01% of DDT, and 0·025% of *Ryania* dust containing 5% rotenone. The toxic symptoms consisted of weakness, tremors, convulsions, and a comatose condition with slow, irregular breathing. Food crops could be safely sprayed, since the insecticidal residues amounted to less than 6 parts per million, which was innocuous.

R. Wien

See also Section Hygiene and Public Health, Abstracts 2215, 2221.

BLOOD TRANSFUSION

2298. **The Value of the Coombs Test in Detection of Isosensitization of the Newborn**

R. Jakobowicz, V. I. Krieger, and R. T. Simmons. *Medical Journal of Australia* [*Med. J. Aust.*] 2, 143–153, Aug. 7, 1948. 18 refs.

This is a report from Melbourne of an investigation in which the direct anti-human-globulin test was applied to 1,580 samples of cord blood. Of 32 positive reactions 24 could be attributed to anti-Rh. No explanation could be found for 5 of the remaining 8, for both Rh and ABO groups of mother and infant were compatible, and all 5 children were healthy and no abnormal antibody was found in the mother's serum. The authors consider that the positive reaction in the remaining 3 may have been due to the ABO incompatibility which was present between mother and foetus. They conclude: "The direct Coombs test appears to be slightly more sensitive than other methods of detecting Rh immunization, although occasional positive reactions are observed in the absence of any clinical or other serological evidence of immunization".

R. R. Race

See also Section Paediatrics, Abstract 2398.

Radiology

2299. **Effect of Flavonoids (Vitamin P) on Mortality from Total Body Roentgen Irradiation**
W. G. CLARK, R. P. UNCAPHER, and M. L. JORDAN. *Science* [*Science*] **108**, 629–630, Dec. 3, 1948. 11 refs.

The authors, working at Scripps Metabolic Clinic, La Jolla, California, report the effect of administering a flavonoid substance to guinea-pigs subjected to median lethal doses of total body *x*-ray irradiation. They conclude that, experimentally, this preparation reduces the mortality rate by about half.

"Calcium flavonate" was prepared fresh daily by precipitation of the alcohol extract of fresh lemon peels in an alkaline medium containing calcium. The precipitate was suspended in water, adjusted to an acid *p*H, reprecipitated by adding alcohol, and filtered. The material was obtained from the filtrate by evaporation. On a weight basis, it gave a cyanidin test about half as intense as rutin and it was free of water, sugars, and hesperidin. Of 71 healthy guinea-pigs receiving a uniform ration with supplementary ascorbic acid (0·2% in drinking water), 45 served as controls and the remainder also had 0·2% "calcium flavonate" added to their drinking water, as previous experiments had indicated that constant ingestion in food or water was the most effective method of administration. After a week of this treatment, the animals were given 220 to 225 r total body irradiation in a single dose, not including back-scatter. For the exposure, controls and treated animals were placed alternately, draught-board fashion, in a multi-compartment wooden box, back-scatter being made uniform by the rice phantom technique of Ellinger (*Radiology*, 1945, **44**, 125). Treatment was continued for the duration of the experiment and clinical symptoms were graded twice weekly with emphasis on visible manifestations of anaemia and purpura. The experiments were terminated after 30 days, when recovery from radiation injury was assumed to be complete. Of 45 controls, 30 (67%) died, half of these within 13 days, but of the 26 treated animals only 9 (35%) died, and haemorrhagic symptoms were much less marked in the latter group.

A. S. McLean

RADIOTHERAPY

2300. ***X*-ray Treatment of Lymphogranulomatosis.** (Die Röntgenstrahlenbehandlung der Lymphogranulomatose) A. VOGT. *Röntgenpraxis* [*Röntgenpraxis*] **17**, 110–116, July, 1948. 4 refs.

In 25 years, 140 cases of lymphogranulomatosis (Hodgkin's disease) have been treated at the *X*-Ray Institute of the University of Tübingen. A tenth of the cases were acute and in these there was no improvement, the average duration of life being 5·4 months. In chronic cases, life could be prolonged on an average for over a year and the majority of patients were able to return to work. With high voltage therapy, death took place 33 to 40 months after the onset of disease and 23 to 32 months after the onset of *x*-ray therapy. In the final cachectic stage *x*-ray therapy to the liver, spleen, and bones had no effect on the course of the disease.

The author used the Holfelder method, administering 1,800 to 2,100 r per skin field in 4 weeks and varying the dose individually on the basis of the erythrocyte sedimentation rate, the temperature during the first treatment, and the absolute and differential counts of leucocytes. Treatment began with superficial doses of 100 to 200 r which were increased to 300 r per field of 10×15 cm. at 150 kV and 15 mA., skin-focus distance 40 cm. and filter 0·5 cm. copper. The dose was reduced if pyrexia occurred. In patients with large mediastinal tumours about two-thirds of the above dose was given to the mediastinum, and no superficial treatment. In recurrence a few doses of 300 r per field were given. Medical treatment was used in late cases as well as irradiation. Teschendorf's distant irradiation method is discussed.

J. Maclean Smith

2301. **Laryngeal Chondronecrosis Following Roentgen Therapy**
W. A. GOODRICH and M. LENZ. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **60**, 22–28, July, 1948. 8 refs.

Necrosis of laryngeal cartilage after *x*-ray therapy occurs only if the cartilage is infected or invaded by carcinoma. Thus it is common in infiltrating or advanced types of carcinoma, but uncommon in the superficial fungating type of growth. The differentiation between necrosis due to radiation and that due to infiltration by disease is often impossible; it is suggested that persistence of oedema of laryngeal mucosa after *x*-ray therapy is a sign of pending necrosis. One of the factors that might accelerate this disaster is biopsy of oedematous, non-ulcerated mucosa after a course of irradiation.

The clinical material in the present report shows an incidence of 28 cases of chondronecrosis out of 205 treated cases; 8 of these patients were apparently free from carcinoma, and of these 2 are still alive 8 and 15 years after treatment. In 2 cases carcinoma was still present, and in the remaining 18 it is not known whether the disease still persisted. Chondronecrosis usually developed within 6 months of the end of the course of treatment, and in most cases the necrosis was so extensive that the site of origin could not be determined. Again, the more advanced the primary lesion the greater the incidence and extent of the necrosis. Irradiation after operations for laryngeal carcinoma seemed to precipitate necrosis, and the authors quote Arbuckle's procedure of subperichondrial resection of the cartilage as a means of overcoming this type of injury. It is suggested that, in

order to minimize the risk of necrosis, the portals of entry should be small, the daily dose should be in the region of 100 r (in air), and the total length of treatment 5 to 7 weeks. Large fields, large daily doses, and a short treatment period may increase the likelihood of oedema and eventual necrosis. The treatment of oedema or established chondronecrosis should be by laryngectomy in selected cases, and penicillin and sulphonamides should be used in all cases. *T. Keith Morgan*

2302. **Roentgen Treatment for Extensive Epithelioma of the Larynx. Results in 139 Cases**
A. U. DESJARDINS, F. A. FIGI, and L. M. VAUGHAN. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **60**, 29–38, July, 1948. 6 refs.

This paper deals with treatment by *x* rays of 139 cases of advanced and inoperable carcinoma of the larynx. The method of treatment was the same in practically every case, by an average tumour dose of 5,300 r through two lateral fields of average size 8 × 12 cm., at 200 kV and with a half-value layer of 1·75 cm. copper. Treatment was given twice daily for 3 weeks, and the surface dose measured in air was 2,000 to 10,000 r per field. It is pointed out that the large size of field used was necessary because the cases submitted to irradiation were of very advanced carcinoma and had been rejected by the surgeons as unsuitable for surgery. The degree of involvement was extensive, 76 patients requiring a tracheotomy before treatment, and the results obtained, which show a 17·8% 5-year survival rate, speak well of this type of treatment in advanced laryngeal cancer.

[No details of incidence of necrosis or of lymph-node involvement are given, neither is there an account of the type of cancer, for example, whether vestibular or not.] *T. Keith Morgan*

2303. **Irradiation in Cancer of the Tongue**
C. P. DONLAN. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **60**, 511–521, Oct., 1948. 7 figs., 26 refs.

The author reviews the treatment of 83 cases of carcinoma of the tongue at the Presbyterian Hospital, New York. Operable cases are described as those in which lesions are small and may be excised with a 1·5 cm. margin of normal tissue, in which there are either no palpable lymph nodes or small ipsilateral mobile nodes, and in which the patient's general condition is good.

The advantages of irradiation in the treatment of this condition are non-impairment of speech, almost negligible mortality, and (more controversial) a higher 3-year survival rate. Interstitial radium application is advised in operable cancer of the anterior two-thirds of the tongue. It is preceded by extraction of carious teeth and a course of chemotherapy. Preliminary external irradiation may also be given in order to reduce the size of the lesion.

The radium needles generally used contain 1·98 mg. radium filtered by 0·5 mm. of platinum, and are 3·2 cm. long, with an active length of 2 cm. The needles are inserted vertically in the tongue, 1 cm. apart and at least 0·5 cm. from the lateral margin in order to prevent over-irradiation of the alveolus with subsequent osteomyelitis. The needles remain in place for 5 to 7 days in order to deliver 8,000 γ r or more, during which time the fluid balance must be kept up and the mouth irrigated 3-hourly. Inoperable lesions of the anterior part of the tongue are treated by interstitial radium or by intra-oral *x*-ray irradiation. In the latter method, a tumour dose of 5,000 r is delivered by means of an intra-oral cone of 3 to 4 cm. diameter. Lesions of the posterior third of the tongue are treated by external irradiation with an 8 × 10 cm. field on each side. Two fields are treated daily, 100 to 150 r (in air) being given in each field, until a 5,000 to 6,000 r tumour dose is delivered. For the treatment of lymph nodes, the author recommends prophylactic neck dissection on the affected side 6 weeks after implantation of needles in the tongue if the primary lesion appears controlled and does not cross the midline. This is carried out whether the mobile nodes are present or not, but the age and general condition of the patient must be taken into account. This choice of treatment is based on the opinion that external irradiation frequently fails to eradicate metastases, whereas neck dissection will save those patients with no clinical evidence of disease but with histological metastases. For fixed nodes in the neck, external irradiation is given to an 8 × 10 or 10 × 15 cm. field at the rate of 200 to 250 r (in air) daily up to 3,500 or 4,000 r. (in air). Use of teleradium or interstitial radium in the treatment of such nodes has been given up, the latter because of the excruciating pain following fibrosis and scarring.

Of 55 patients 17 survived for 5 years or more; of 19 with operable lesions included, 10 survived for over 5 years. The author notes a longer duration of symptoms in the operable group (average 9·25 months for 22 cases) compared with the inoperable group (average 7·5 months for 34 cases), a result not generally expected. *Basil A. Stoll*

2304. **Precision Dosage in Interstitial Irradiation of Cancer of the Cervix Uteri**
J. A. CORSCADEN, S. B. GUSBERG, and C. P. DONLAN. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **60**, 522–534, Oct., 1948. 13 figs., 16 refs.

The authors suggest that intracavitary radium application combined with external irradiation by deep *x* rays does not deliver an adequate dose to the lateral parametrium in the treatment of carcinoma of the cervix uteri. They consider that interstitial application of radium checked by precision stereoscopic radiographs is preferable. It is suggested that a dose of 7,000 γ r is necessary to destroy a cancer cell without severely injuring the normal tissues, while a dose of 15,000 γ r causes destruction of all tissues with sloughing.

After experimentation, the following technique was evolved. In the uterine cavity three tubes are placed, each containing 10 mg. of radium, 2·3 cm. long (active length 1·25 cm. and 1 mm. platinum filter). Around this, in a circle of radius 1·5 cm., are placed in stockade fashion 8 needles each containing 1·98 mg. radium, length

3·2 cm. (active length 2 cm., 0·5 mm. platinum filtration). At a distance of 1·5 cm. lateral to the stockade on each side are placed 2 needles 1 cm. apart in a sagittal plane, each containing 1·98 mg. radium as before. Finally at a distance of 1·5 cm. lateral to these sources (that is at 4·5 cm. from the cervical canal) are placed 5 needles parallel to the pelvic wall and 1 cm. apart, each containing 4·8 mg. of radium, length 6 cm. (active length 5 cm., filtration 0·5 mm. platinum). The duration of the treatment is 120 hours. The technique in relation to the anatomy of the pelvis is described in some detail in the paper.

On the day after the operation a precision stereoscopic radiograph of the pelvis is taken, and from the Paterson and Parker table the dosage at various points is calculated. With the arrangement described, the dose at the cervical mass is 11,010 γ r, in the parametrial region at 3 cm. from the cervical canal 14,346 γ r, and in the lateral parametrium near the pelvic wall 10,803 γ r. The authors suggest that by the use of more needles of lower intensity a still more homogeneous dosage can be achieved.

The principal objection to the method is that it is blind and that the needles are likely to injure the intestine, bladder, ureter, or larger arteries. The authors consider the risk negligible with a precise knowledge of the anatomy of the pelvis and with the use of blunt needles. Another difficulty is that, if the vaginal wall is distorted, the method of introduction and the pattern may require modification. Infection occurs occasionally when needles are plunged through a necrotic mass.

The number of cases treated by the method and the results obtained are not stated but all cases treated were classified as of stage III (League of Nations classification). The authors claim that the immediate results are striking and superior to those of the intracavitary technique.

Basil A. Stoll

2305. **Radiation Injuries Produced by Contact Roentgen Therapy.** [In English]
E. Poppe. *Acta Radiologica* [*Acta radiol., Stockh.*] **30**, 365–370, 1948. 3 refs.

A series of 1,384 patients with skin lesions, mostly benign, were treated by means of a Philips apparatus with a target-skin distance of 18 mm. unfiltered, 20 mm. with additional filter, 2 mA, 50 kV, and a maximal field 20 mm. in diameter. The depth dose at 5 mm. was 40% and at 1 cm. 20%. Small skin cancers responded to a single dose of 4,000 to 5,000 r but left a disfiguring scar; these are better treated by radium. In 17 cases of benign lesions, all on fingers and toes, there were severe reactions leaving swollen tender fingers for many months with residual damage to the skin. In a further 7 cases necrotic ulcers resulted. One of these patients received a second dose for a residual lesion, while in 5 of the others the ulcer was on a finger or toe and resulted from doses of 3,000 to 7,000 r.

The author recommends that special care should be taken to fractionate the treatment of warts on fingers and toes, and that no extra filter be added, as this increases the depth dose. Lesions which occur on scars or poorly nourished skin or which have previously been irradiated should be treated by electrocauterization and not by contact therapy. He suggests that an apparatus operating at a lower voltage, such as 20 kV, with which a much lower depth dose could be obtained would be an advantage.

D. G. Bratherton

RADIODIAGNOSIS

2306. **Intravenous Cholecystography with Tetraiodophthalic Fluorescein**
G. E. Moore and M. J. Smith. *Surgery* [*Surgery*] **24**, 17–21, July, 1948. 4 figs., 8 refs.

The advantages claimed for this new dye are that it can be safely injected intravenously in as small a volume as 15 ml. given in 2 minutes, and that no very serious results ensue if some leaks out into the subcutaneous tissues. A normal gall-bladder shadow was demonstrated in 2 patients within 15 minutes, but a 2-hour delay is recommended as a routine. Only 22 cases are reported in the present paper and studies are still in progress with dye containing radioactive iodine. [The method promises to be valuable.]

Denys Jennings

2307. **Observations on the *X*-ray Visualization of the Pancreatic Duct.** (Ein Beitrag zur röntgenologischen Darstellung des Ductus pancreaticus)
H. Stiller. *Röntgenpraxis* [*Röntgenpraxis*] **17**, 18–23, June, 1948. 3 figs., 34 refs.

In 10% of cases cholangiography by various methods rapidly reveals the pancreatic duct because of spasm of the sphincter or the presence of a stone when a joint duodenal opening for the bile and pancreatic ducts is present. The gross and detailed anatomy of the ducts is discussed. In a case with separately opening ducts, post-operative cholangiography was performed through an indwelling T-tube, thorotrast and cineradiography being used. The observations of von Bernhard on the function of the sphincter of Oddi were confirmed and the pendulum movements of the duodenum were noted. Retrograde filling of the pancreatic duct occurred when the sphincter of Oddi was relaxing. Both sphincters relaxed together, the pancreatic duct emptying suddenly and the bile duct slowly. The former refilled towards the end of bile-duct emptying to a degree varying with sphincter contraction and intraduodenal pressure. The author considers that cases of acute necrosis of the pancreas or pancreatitis occurring without gall-stones are due to the presence of a separately opening pancreatic duct with a weak sphincter.

J. Maclean Smith

2308. **A New Type of Bronchographic Finding in Chronic Purulent Bronchitis.** (Ein neuartiger bronchographischer Befund bei der chronischen eitrigen Bronchitis)
E. Stutz. *Röntgenpraxis* [*Röntgenpraxis*] **17**, 91–93, July, 1948. 1 fig.

The author describes bronchographic findings in a case of diffuse cylindrical bronchiectasis. With the

patient in the standing position small saccular fillings 1 to 4 mm. deep to the bronchial lumen and 1 to 2 mm. across were seen close to one another in the walls of the main bronchi. They disappeared on coughing. The patient died and at necropsy a marked chronic purulent bronchitis was present. From the histology it was considered that a progressive necrotizing process of the ducts of the mucosal glands had led to the formation of ectatic ducts communicating with the lung substance. These ducts may have been blocked by viscid secretion, producing the appearances described, which are considered to be signs of graye inflammation of the bronchial wall. *J. Maclean Smith*

2309. **Subdural Air Shadows and Cortical Atrophy.** (Ombres gazeuses sous-durales et atrophie corticale)
P. MARTIN and W. GEETS. *Acta Neurologica et Psychiatrica Belgica* [*Acta neurol. psychiat. belg.*] **48**, 493–501, Oct., 1948. 4 figs., 5 refs.

The authors point out that subdural air shadows have been studied chiefly by Penfield and Norcross, who found that, of 22 cases in which air encephalography was carried out, subdural air was present in 10; 7 of these patients were cured of their symptoms. The present authors set out to confirm these findings: they investigated 58 cases, in 7 of which there was subdural air. Many of the patients had symptoms due to cranio-cerebral injuries but none was cured of his symptoms by injection of air. The differentiation between subdural air and subarachnoid air is discussed, as well as the methods by which air enters the subdural space. In this connexion three possibilities are suggested: (1) that the entrance of air is facilitated by permeability of the arachnoid membrane; (2) that a tear in the arachnoid allows free passage of air; or (3) that air is introduced by lumbar subdural injection. There is no question that the last of these three can happen, but there is doubt about the first two possibilities. *J. W. Bull*

2310. **Reflux into the Canal of Wirsung During Cholangiography. Dystonias of the Canal of Wirsung.** (Le reflux dans le canal de Wirsung au cours des cholangiographies. Dystonies du canal de Wirsung)
P. MALLET-GUY, E. GUILLET, and L. DURAND. *Lyon Chirurgical* [*Lyon chir.*] **43**, 653–676, Nov.-Dec., 1948. 17 figs., 27 refs.

It is still undecided whether there is any significance in the regurgitation of contrast material into the main pancreatic duct during cholangiography. In this paper the relevant literature is reviewed and an attempt is made to draw some conclusions from a large personal material of 800 cholangiographies. [The statistics are unfortunately not clearly set out.] One or more exposures seem to have been made as a routine during the course of gall-bladder operations, while further exposures were made at some time in the post-operative period after injection of opaque material into the T-drain in the common bile duct. In 173 patients there was definite evidence of regurgitation. This was seen in 209 out of 357 films taken during operation, and in 125 out of 407 films taken in the post-operative period. In 972 exposures on 627 patients during operation and in 1,090 exposures on the same patients after operation, there was no regurgitation. Except in some of the earliest cases, manometric pressure readings were taken as a routine while radiography was being carried out.

The type of anaesthesia is believed to be important, and use of any substance which might interfere with the tone of the sphincter of Oddi must be avoided. Spinal analgesia is open to objection because the sympathetic is blocked. Morphine and thiopentone must also be avoided. Observations made during operation under local analgesia or general ether–oxygen are believed to be the most reliable. In the post-operative period, regurgitation may no longer be present and it is believed that this is because the reflex irritation due to stones has been removed. The nature of the contrast material is unimportant and, provided sufficient is injected, it makes no difference whether the injection is made into the gall-bladder or directly into the common duct. The pressure with which the injection is made seems to have no influence in causing a reflux, though it does alter the amount which flows into the pancreas if any reflux is present.

Since a reflux is never found with a healthy pancreas and biliary tract, the authors believe that the finding has some pathological significance. The causes of reflux are classified as follows. In 12 cases there was a mechanical obstruction at the ampulla of Vater. In 53 cases there was hypertony of the sphincter of Oddi. In this group reflux never appeared after sphincterotomy or when the duct pressure failed to rise. In 36 cases there was hypotony of the sphincter of Oddi and this was usually associated with a dilated duct of Wirsung. The contrast material flowed equally readily into the duodenum and into the pancreas. In 40 cases there was a chronic pancreatitis and in 2 cases an acute pancreatitis. In 19 cases there were gall-stones or cholangitis, in 3 cases there was an acute cholecystitis, and 8 cases could not be classified for lack of manometric control.

[There is some anatomical evidence that an arrangement of the ducts which allows pancreatic juice to regurgitate into the bile ducts, and bile to regurgitate into the pancreas, is relatively common in pancreatitis and cholelithiasis. The present paper seems to support the idea that regurgitation occurs and is important, but the statistics are so incomplete that it is impossible to assess the validity of the argument.] *Denys Jennings*

2311. **Tomographic Study of Mediastinal Tumours.** (Contributo allo studio stratigrafico dei tumori mediastinici)
V. AZIO. *Archivio di Radiologia* [*Arch. Radiol.*] **22**, 87–103, Nov., 1948. 9 figs., 6 refs.

The author discusses the anatomy and the radiological and tomographic appearances of the normal mediastinum. He describes those tomographic characteristics of mediastinal tumours which are useful for the differential diagnosis of the various types of tumour. *A. Orley*

Pathology

2312. **Effect of Heparin and Dicoumarol on Sludge Formation**
H. LAUFMAN, W. B. MARTIN, and C. TANTURI. *Science* [*Science*] **108**, 283–284, Sept. 10, 1948. 4 refs.

Microscopical observation of small peripheral arteries and veins in the exposed mesentery of dogs showed that the blood corpuscles began to form a sludge 10 to 20 minutes after the portal or superior mesenteric vein was clamped. As the stream slowed and anoxia increased, groups of the agglutinated corpuscles attached themselves to the endothelium of the vein, which sooner or later became occluded by thrombus. Neither heparin nor dicoumarol administered in clinically safe but effective doses prevented sludge formation but they did prevent thrombosis and the adhesion of the sludged masses of cells to the vessel wall. *Douglas H. Collins*

2313. **The Histological Effects of Nitrogen Mustards on Human Tumours and Tissues**
S. SPITZ. *Cancer* [*Cancer*] **1**, 383–398, Sept., 1948. 20 figs., 16 refs.

This is a post-mortem study of 57 cases which had been treated with nitrogen mustards, and most of which had previously been given other forms of treatment, including surgery and irradiation; many of them had been considered inoperable. The duration of illness did not differ from that in untreated cases. During the terminal phases of the illness transfusions, penicillin, streptomycin, and sulphonamides were given. Purpura was common, and intestinal or cerebral haemorrhage was a frequent termination. The femoral, sternal, costal, and vertebral marrow was studied as well as routine sections.

In 2 of 12 cases of Hodgkin's disease the cells showed a vacuolated cytoplasm and swollen nuclei with an ill-defined chromatin structure, or a more pleomorphic cell picture than in the biopsy material. In others the cytological changes were not prominent except for reduction in cellularity. In 12 cases of reticulum-cell sarcoma, reduced cellularity and pyknosis were seen, most prominently in a patient who had received nitrogen mustard 18 hours before death. In cases in which death occurred 12 to 21 days after treatment the normal structure of glands became evident once more, especially the sinuses. Later cases showed little change. In the 4 cases of lymphosarcoma the changes were similar to those in 9 cases of lymphatic leukaemia. Where the leucocyte count remained high, the histology of biopsy and necropsy material showed no changes due to treatment. In 4 cases in which a fall in the leucocyte count occurred there was some degree of " restitution of the previously masked architecture." No histological evidence of therapy was found in 4 cases of myeloid leukaemia. In 2 cases leukaemic infiltration in marrow and viscera was reduced. The marrow was fatty and myxomatous, and only megakaryocytes and a few other cells remained. No significant changes were seen in 13 cases of inoperable or recurrent malignant tumours.

In 15 of 22 cases in which the marrow was examined there was hypoplasia, most prominent in the granulocytic cells, and in 12 cases aplasia was almost complete. In 12 non-leukaemic spleens the follicles could not be identified, there were few lymphocytes, and in the red pulp focal necroses were seen. Of 30 tests, only 3 showed active spermatogenesis. Liver, adrenals, and kidneys showed no changes referable to mustard therapy. In the intestines the lymphoid elements were reduced.

The " blistering " or ballooning of cells was the outstanding feature in this series. Sudanophil droplets were seen in phagocytes and reticulum cells, especially in Hodgkin's disease. *E. Neumark*

2314. **Atypical Amyloid Disease, with Observations on a New Silver Stain for Amyloid**
L. S. KING. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 1095–1115, Sept., 1948, 6 figs., 39 refs.

The author classifies amyloid into typical and atypical entirely on the basis of its distribution. It is typical when it affects the usual abdominal viscera, and atypical when it affects none (or only one) of these organs and is mainly situated elsewhere. There are about 50 cases in the literature of so-called primary amyloidosis (cases without any obvious infective or other cause), and the author adds 5 more. A case of amyloidosis associated with chronic pyelonephritis is also described. Details are given of a new silver method of staining amyloid in frozen sections. *D. M. Pryce*

2315. **Nucleic Acids and Cytologic Changes in Regenerating Rat Liver**
R. E. STOWELL. *Archives of Pathology* [*Arch. Path.*] **46**, 164–178, Aug., 1948. 4 figs., 28 refs.

The author made a detailed study of minute cellular and biochemical changes in rat livers after extirpation of more than half of the organ. Within the first 6 hours of regeneration the liver cells showed an increase in visible cytoplasmic lipids. The volumes of cytoplasm, nucleus, and nucleolus began to increase within 6 hours, reached respective maxima of 2·6, 2·2, and 4·1 times the normal at about 24 hours, and thereafter decreased as increased cell division began. After 48 hours' regeneration the mean nuclear and cytoplasmic volumes were still considerably above normal, whereas the mean nucleolar volume was lower. There was little change in nucleic-acid concentration during the first 24 hours of regeneration, but thereafter rapid cell division was accompanied by an increase of nucleic-acid concentration in the cytoplasm adjacent to the nucleus and also in the nucleoli. *Martin Hynes*

EXPERIMENTAL PATHOLOGY

2316. **Mitotic Activity in the Aortic Lesions of Experimental Cholesterol Atherosclerosis of Rabbits**
G. C. McMillan and G. L. Duff. *Archives of Pathology* [*Arch. Path.*] **46**, 179–182, Aug., 1948. 1 fig., 5 refs.

The observed frequent occurrence of mitotic figures in the foam cells and fibroblasts of the aortic intimal lesions of experimental cholesterol atherosclerosis of the rabbit is interpreted as evidence that a considerable proportion, if not all, of these cells arise *in situ* by mitotic division. [Authors' summary.]

2317. **Hepatic Riboflavin and Tumor Formation in Rats Fed Azo Dyes in Various Diets**
A. C. Griffin and C. A. Baumann. *Cancer Research* [*Cancer Res.*] **8**, 279–284, June, 1948. 18 refs.

It is well recognized that rats given *p*-dimethylaminoazobenzene (DAB) or *m'*-methyl-*p*-dimethylaminoazobenzene (*m'*-Me-DAB) develop tumours at rates that depend upon the composition of the basal diet. In one set of experiments reported here diets were designed to show the relative effectiveness of ribroflavin, hydrogenated coconut oil, and the rice bran concentrate " vitab " in altering the rate of formation of tumours due to DAB. Groups of rats varying in number from 9 to 15 were fed for 15 months on a concentration of 0·06% of the dye in the ration. In the other set of experiments, groups of rats ranging from 3 to 6 in number were fed on either DAB or *m'*-Me-DAB in various diets for 3 to 6 weeks and thereafter the riboflavin content of the livers was analysed. The authors' summary of the results is as follows [but due regard must be taken of the small numbers of animals used in each group]. " Hepatic tumors due to DAB developed more rapidly on a diet containing the rice bran concentrate, ' vitab ', than on a standard synthetic diet. The two diets contained 0·7 and 2·0 mg. of riboflavin per kg., respectively. When the riboflavin content of the two diets was equalized, tumor formation was also equal. Reduction in riboflavin intake on both diets accelerated tumor formation. When DAB was fed to rats in the ' vitab ' diet low in riboflavin, the concentration of this vitamin in the liver tended to decrease more rapidly than when the control synthetic diet was fed. The addition of riboflavin to either diet increased hepatic retention of the vitamin and decreased tumor incidence. Thus, retention of riboflavin in the liver paralleled resistance to tumor formation with this carcinogen. When *m'*-Me-DAB was fed in the ' vitab ' and synthetic diets respectively, the amounts of hepatic riboflavin retained were equally low. These diets do not affect the rate at which tumors develop when *m'*-Me-DAB is fed. Livers of rats fed DAB in hydrogenated coconut oil contained more riboflavin than when corn oil was fed. The coconut oil retards tumor formation by this dye. However, when *m'*-Me-DAB was fed in the two oils, the amounts of hepatic riboflavin were equally low; tumor formation due to *m'*-Me-DAB is essentially the same on both oils. The addition of 10 mg. of riboflavin per kg. of diet resulted in a marked increase in hepatic riboflavin when the carcinogen was DAB, but in only a moderate increase in the presence of *m'*-Me-DAB. Riboflavin is more effective in retarding tumor formation due to the former dye than to the latter. These results, and the observation that the degree of carcinogenicity of various azo dyes parallels their effectiveness in lowering hepatic riboflavin, suggest the general conclusion that there is an inverse relation between the rate of tumor development and the level of hepatic riboflavin maintained on any particular dietary regimen." *G. M. Bonser*

2318. **Lack of Extractable Carcinogens in the Skin of Patients with Multiple Precancerous Keratoses of Actinic Origin**
F. E. Mohs. *Cancer Research* [*Cancer Res.*] **8**, 371–375, Aug., 1948. 11 refs.

Is the skin cancer produced by ultraviolet light due to the formation, within the tissues, of substances resembling the carcinogenic hydrocarbons? To test this possibility the skin of patients with multiple precancerous keratoses of actinic origin was repeatedly washed with benzene and the extractable material was tested for carcinogenic activity in rats and mice. Mainly elderly people with multiple keratoses in which at least one carcinoma had arisen were instructed to wash one side of their face with benzene applied on gauze pads and to preserve the pads in a large bottle. This procedure was repeated from 20 to 706 times. The pads were extracted with hot benzene for 8 hours in a Soxhlet apparatus, the benzene was removed, and the remaining thick yellow or brown oil used for tests of carcinogenicity. Small amounts of skin washings and excised keratoses from 25 patients were pooled and also extracted with benzene. Mice received skin paintings of the residual oil with or without croton oil or irradiation with ultraviolet light, and the oil was also injected subcutaneously into rats and mice. Unextracted senile keratoses were also implanted subcutaneously into rats. All these procedures failed to demonstrate the presence of any extractable carcinogenic substance. The repeated washing of precancerous skin with benzene in no way affected the incidence of cancerous change in the keratoses. *H. G. Crabtree*

2319. **The Effect of Carcinogenic Compounds on the Ascorbic Acid Content of the Liver in Mice and Rats**
M. Daff, C. Hoch-Ligeti, E. L. Kennaway, and M. M. Tipler. *Cancer Research* [*Cancer Res.*] **8**, 376–380, Aug., 1948. 9 refs.

The effect of some carcinogenic and non-carcinogenic compounds on the concentration of ascorbic acid in the liver of mice has been previously recorded (*Cancer Res.* 1944, **4**, 367). This investigation has now been extended to the following compounds: *p*-dimethylaminoazobenzene (*p*-DA), 2-acetamidofluorene (AAF), 7-hydroxy-2-acetamidofluorene (7-OH-AAF), and azobenzene (AB). In some experiments CBA mice and Wistar and black-and-white rats received subcutaneous or intraperitoneal injections of AAF or 7-OH-AAF, and the ascorbic acid

content of the liver was estimated 6 to 13 days later. In other experiments lasting up to 460 days Wistar rats were fed on a semi-synthetic diet permitting growth or on a rice diet preventing growth which contained one or other of the four tested compounds. The homogenized liver was extracted with 3% metaphosphoric acid and titrated with 2 : 6-dichlorophenolindophenol. After injection, black-and-white rats responded to AAF by an increased concentration of ascorbic acid in the liver, but this effect was much smaller in Wistar rats. Similarly, in CBA male mice an increase of ascorbic acid took place, but in the females it did not; this sexual difference was not found in rats. 7-OH-AAF was almost or quite inactive both in rats and in male mice. Wistar rats fed on the semi-synthetic diet containing *p*-DA or AAF had an increased liver content of ascorbic acid, but the effect was smaller with 7-OH-AAF. A similar increase was found in the liver of rats on a rice diet containing *p*-DA or AB.

In the discussion of the possible significance of these results a summary is given of all the work so far done on these lines. *H. G. Crabtree*

2320. **Observations on the Hepatotoxic Action of the Carcinogen *p*-Dimethylaminoazobenzene**

J. W. Orr and D. E. Price. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 461–469, July, 1948. 12 figs., 11 refs.

In stock rats maintained on a mixed diet of grain, bread, and rat cake intraperitoneal injection of *p*-dimethylaminoazobenzene in amounts exceeding 250 mg. per kg. was lethal in less than 3 days. The animals survive a dose of 150 mg. per kg. intraperitoneally in lard and over 95% of the drug is absorbed in 24 hours. Multiple doses of 100 mg. per kg. 3 times a week or of 50 mg. per kg. 6 times a week may be administered with survival of some animals for more than 38 days. The toxic effects appear to be attributable to liver damage. With large doses degenerative changes are most marked at the centres of lobules. With smaller doses the degenerative changes are more diffuse and less intense and are followed by reparative proliferation of the hepatic parenchyma, bile ducts, and connective tissue. The histological course of these lesions is described.

L. A. Elson

2321. **Influence of Thiouracil on Carcinoma Induced by 2-Acetaminofluorene**

K. E. Paschkis, A. Cantarow, and J. Stasney. *Cancer Research* [*Cancer Res.*] **8**, 257–263, June, 1948. 6 figs., 15 refs.

Studies are reported of: (1) the protective action of thiouracil against hepatic lesions caused by 2-acetylaminofluorene (AAF) and the effect of methionine thereon; (2) the effect of simultaneous administration of sex hormones on this protective action; (3) the effects on the thyroid gland of simultaneous administration of AAF and thiouracil; and (4) the effect of thiouracil on the development of liver cancer by *p*-dimethylaminoazobenzene (DAB).

Rats of the Sherman strain (Wistar descendants), weighing 75 to 100 g., were given 0·03% of AAF in a corn-meal diet (16% protein), reinforced by powdered brewer's yeast. When DAB was the carcinogen, it was given in a high-fat diet (20% corn oil). Thiouracil was administered in the drinking water (0·05 or 0·1%) as was methionine (0·4%) and the sex hormones were injected in oil solution thrice weekly, as was *l*-thyroxine in watery solution. Although 395 rats were used in all, there were so many different groups that some contained only 6, 8, or 12 rats.

The incidence of hepatic carcinoma was much reduced in both sexes by thiouracil and also in males treated with testosterone. The androgenic effect of the hormone was, however, less in the group treated with AAF than in the group treated with AAF and thiouracil. The effect of thiouracil on DAB hepatic carcinoma in females was similar, but there was no reduction in such hepatic carcinoma in males. Methionine had no effect, with or without testosterone.

The thyroid was increased in weight and size in all rats receiving thiouracil, and irregular nodular areas were observed within the hyperplastic thyroid tissue. The latter were more frequent and extensive in animals receiving AAF as well and the incidence of thyroid carcinoma was tripled, thus confirming Bielschowsky's original observation (*Brit. J. exp. Path.*, 1944, **25**, 90). Administration of sex hormones had no influence on the thyroid tumours thus induced.

The possible mechanisms whereby the protective action of thiouracil on liver tumours may be produced are discussed. The possibility that hypothyroidism plays an important part cannot be eliminated, for, in attempts to give thyroxine, amounts adequate to prevent thyroid hyperplasia in thiouracil-treated rats were not adequate when thiouracil and AAF were given together.

G. M. Bonser

2322. **Oestrogen-induced Fibroids of the Thoracic Serosa**

S. Bruzzone, H. Elgueta, R. Iglesias, and A. Lipschutz. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 267–272, Sept., 1948. 5 figs., 10 refs.

Attempts were made to discover why abdominal fibroids are readily produced by continued oestrogen administration to guinea-pigs, but thoracic reactions occur only rarely.

Communication was established between the thoracic and abdominal cavities by punching out a circle 1·5 to 2 cm. in diameter from the diaphragm. An abdominal approach was used; 39 out of 66 animals survived for more than a month. Thirty days after operation a tablet of diethylstilboestrol and cholesterol or of oestradiol dipropionate was implanted subcutaneously. Eighteen animals survived for more than 96 days; at necropsy all had abdominal fibroids and in 7 there was in addition a thoracic fibrous reaction. Two of the 7 had tumours of the diaphragm. Histologically the thoracic tumours were identical with the abdominal oestrogen-induced fibroids.

To eliminate mechanical stimuli from prolapse of liver or intestines as the cause, in 10 animals a metal

tablet was introduced into the thoracic cavity and another into the abdominal cavity together with a subcutaneous tablet of oestrogen. Only one thoracic reaction comparable to the abdominal tumours appeared. In another 14 animals a tablet of oestradiol or oestradiol dipropionate was inserted into the thoracic cavity; in 12 abdominal tumours developed but no thoracic tumours were found.

It is concluded that the tumoral reaction of the abdominal cavity is mediated by an internal ambiental factor normally present in the abdominal serosal fluid. The absence of this factor presumably protects against thoracic tumour production. *G. Calcutt*

2323. **The Role of Initiating and Promoting Factors in the Pathogenesis of Tumours of the Thyroid**
W. H. HALL. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 273–280, Sept., 1948. 6 figs., 18 refs.

Experiments were carried out to determine whether initiating and promoting factors are involved in tumour formation in tissues other than skin. The thyroid was the organ selected and acetylaminofluorene the carcinogen.

Rats of a Wistar strain received 4 to 6 doses each of 2·5 mg. of carcinogen in a watery suspension by stomach tube over a period of 1 week. Experimental animals and controls received 4-methyl-2-thiouracil as a 0·01% solution in drinking water for prolonged periods. In rats killed at intervals up to 21 weeks there were no macroscopic differences in the thyroid, but microscopically a progressively increasing number of adenomata was found in experimental animals at periods after 10 weeks. There were no indications of malignancy. In a few controls, killed at intervals up to 42 weeks, single adenomata were present. Some rats which had received the carcinogen were also given desiccated thyroid during the latter weeks, the methylthiouracil being continued. No signs of regression or necrosis were found but the thyroid-treated animals had glands with low epithelium and full of colloid, and adenomata containing frequent colloid cysts lined with low cuboidal or flat epithelium, while the others had the high epithelium of hyperplastic tissue and adenomata with only occasional colloid cysts.

In a further experiment 20 female rats received 6 mg. of allylthiourea daily for 18 weeks and then 4 mg. of acetylaminofluorene daily for 25 weeks. There was no indication that the goitrogenic agent increased susceptibility to the carcinogen. In another experiment 14 rats received 4 doses of 2·5 mg. of acetylaminofluorene, and methylthiouracil administration began at intervals of 4 to 18 weeks later. All animals receiving methylthiouracil for more than 13 weeks even after an interval of 18 weeks had multiple adenomata.

Since the action of the so-called goitrogenic agents is mediated through the thyrotropic hormone of the pituitary it is concluded that in these experiments the thyrotropic hormone plays the same part in the pathogenesis of multiple adenomata of the thyroid as do cocarcinogens in the pathogenesis of papillomata of the skin. *G. Calcutt*

2324. **Tissue Changes in Mice Treated with Pentose Nucleotides and Related Compounds**
T. H. BARAKAN, G. R. BARKER, J. M. GULLAND, and L. D. PARSONS. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 441–459, July, 1948. 12 figs., 21 refs.

Results are given of an examination of the tissue changes produced in tumour-bearing, normal, or irradiated mice by injection of yeast purine and pyrimidine pentose nucleotides, either singly or in various combinations. Adenylic (I) and guanylic (II) acids inhibited the growth of mouse tumours [a methylcholanthrene tumour grafted in C57 mice], while cytidylic acid (III) had negligible action, and uridylic acid (IV), also uridine and uracil, a growth-stimulating effect. In combination, I and II had an increased inhibitory action, but mixtures of either with IV were without activity. Similarly a mixture of I and III produced considerable inhibition but II and III did not.

Histological examination of the spleens of tumour-bearing mice treated with I, II, or III showed increases in iron-reacting material, whereas IV (and uridine or uracil) caused a diminution in these deposits. In normal mice injection of I, III, IV, uridine, or uracil caused a rise in the total white blood cell count, but II did not. In combination, II and IV, or III and the sodium salt of IV, produced a considerable leucocytosis. A mixture of I and II had the same effect as II alone, whereas I and III together gave only a moderate leucocytosis. Tissue changes produced by similar treatment of irradiated mice [single *x*-ray doses of 250 to 450 r] paralleled those in normal mice. Histological changes in the lymph nodes of mice treated with nucleotides resembled those hitherto described (Parsons, *J. Path. Bact.*, 1938, **47**, 501) for the lymph nodes of mice either irradiated or treated with carcinogens or bearing primary or grafted sarcomata.

The possible functions of the nucleotides as endocellular inhibitors of normal cell growth, and in the maintenance of normal cell metabolism, are discussed.
R. J. C. Harris

2325. **Adrenal Changes in Animals Bearing Transplanted Tumours**
K. SAVARD. *Science* [*Science*] **108**, 381–383, Oct. 8, 1948. 7 refs.

The work described in this preliminary note on the changes observed in the adrenal and thymus glands of mice bearing the transplantable tumour "sarcoma 180" was suggested by clinical and experimental evidence of a relation between neoplasms and adrenal dysfunction. Tumour tissue was implanted in 46 young adult female mice of Carworth Farm CFW strain, and the same number served as controls. Groups were killed on the 6th, 9th, and 12th days, food being denied on the day before death. The weights of the tumours, thymus, and adrenals, together with the ascorbic acid content of the adrenals, are tabulated. They indicate that, with increasing tumour size, there is a progressive adrenal hypertrophy and thymus involution. After the 6th day the level of ascorbic acid fell continuously, being little more than half its normal value on the 12th day.

The results are interpreted in terms of a "general adaptation syndrome", the tumour acting as a non-specific stimulus through the pituitary and inducing the changes observed, though the possibility of a direct action of the tumour on the adrenals and thymus cannot be excluded. Final interpretation is reserved until observations on inbred strains of mice bearing spontaneous tumours are made. *H. G. Crabtree*

2326. **Haemagglutination by Extracts of Tumours and of Some Normal Tissues**
M. H. SALAMAN. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 253–267, Sept., 1948. 17 refs.

Tissue was ground in Ringer solution or buffered saline to give a 10 or 20% suspension, centrifuged at moderate speed, and the supernatant used. Tumours used included C 57, S 37, and Crocker 180 sarcomata, C 57 mammary adenocarcinomata, D 13 thymoma, Walker 256 carcinoma, and a primary hepatoma. Mouse, rabbit, horse, sheep, rat, guinea-pig, human, and fowl red cells were used for haemagglutination tests. Haemolysis was slight except at 37° C. or after 24 to 48 hours at room temperature.

The haemagglutinating power of tumour extracts fell rapidly on standing, usually completely disappearing in 24 hours at room temperature. In the case of C 57 sarcoma this decline was not prevented by 0·08% sodium azide, 0·0001 to 0·003 M sodium iodoacetate, neutralized 0·002 M sodium cyanide, neutralized 0·01 M ascorbic acid, 0·01 M hydroquinone, and bright iron. Decline of activity was as rapid in an oxygen-free atmosphere as in air. Cysteine and glutathione both retarded the decline appreciably; 0·01 M sodium thioglycollate and 0·01 M BAL were more efficient. BAL would also restore activity to inactive extracts. The haemagglutinating titres of extracts varied considerably; the sarcomata gave higher titres than the carcinomata. Extracts of liver, spleen, kidney, heart, lung, brain, voluntary muscle, lymph node, and thyroid from both normal and tumour-bearing mice were inactive with mouse red cells. Extracts of adult mouse testicle, ovary, uterus, voluntary muscle, and whole mouse embryo and placenta agglutinated rabbit red cells and sometimes mouse cells. Generally, titres were lower than those of mouse sarcomata extracts. The activity of these extracts was preserved or restored by BAL in the same way as that of tumour extracts.

The haemagglutinating agent was not inhibited by normal serum or sera from mice in which tumours had regressed. Haemagglutination was accelerated by rise in temperature, but addition of complement had no detectable effect. The haemagglutinating agent was absorbed by those cells agglutinated by it. The agent passed through "gradocol" membranes and Berkefeld V candles with only slight loss of activity, but was not dialysable through "cellophane". It was precipitated by $\frac{1}{3}$ to $\frac{3}{4}$ saturation with ammonium sulphate, and inactivated at 100° C. in 10 minutes at *p*H 6 and 9. In the absence of BAL it was irreversibly inactivated by digestion with trypsin or papain at 37° C. in one hour. Addition of BAL prevented any loss for up to 2½ hours. Incubation with lecithinase had no detectable effect. Copper sulphate, and manganese, cobalt and ferric salts rapidly destroyed activity, this being partially recoverable by subsequent addition of BAL. Activity was destroyed by hydrogen peroxide, sodium hypochlorite, and iodine, partial restoration occurring on addition of BAL.

It is suggested that the haemagglutinating agent of tumours is a readily oxidizable substance only active in the reduced state. It may be a sulphydryl compound, although evidence on this point is not definite.
G. Calcutt

2327. **Urethane and Experimental Amyloidosis of Mice.** (Urethan und experimentelles Mäuseamyloid)
G. SCHETTLER. *Zeitschrift für die Gesamte Innere Medizin* [*Z. ges. inn. Med.*] **3**, 557–564, Sept., 1948. 37 refs.

The conclusion drawn from the work described in this long paper is that prolonged parenteral administration of urethane to mice delays or prevents the experimental production of amyloid. If deposition of amyloid is an antigen-antibody phenomenon, the inhibitory effect of urethane may result from damage to mesenchymal and perhaps parenchymal cells. *A. Piney*

2328. **The Effect of Nutrition on the Tumor Response in Rous Chicken Sarcoma**
P. A. LITTLE, J. J. OLESON, and Y. SUBBAROW. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1139–1143, Sept., 1948. 5 refs.

Suspensions of Rous sarcoma tissue were prepared from tumour stored in a dry-ice chest, and doses of 0·25 ml. containing 1 mg. of tissue were injected into day-old chicks. The development of tumours was observed in groups of chicks fed on a basal diet with or without various nutrients. Vitamins A, D, E, and K, *p*-aminobenzoic acid, and biotin had little effect on the development of tumours. Riboflavin and cholic acid increased the number of tumours without changing the rate of growth; about three times as many tumours developed when these nutrients were supplied as when they were withheld. Nicotinamide and calcium pantothenate accelerated the growth of tumours but had less effect on the total incidence. Folic acid had the greatest effect and was the only essential nutrient among those tested; its withdrawal prevented tumour development.
L. Foulds

2329. **The Use of Antagonists of Pteroylglutamic Acid in Controlling Rous Chicken Sarcoma**
P. A. LITTLE, A. SAMPATH, and Y. SUBBAROW. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1144–1149, Sept., 1948. 9 refs.

It was found previously that folic acid stimulated the growth of Rous sarcoma whereas antagonists of folic acid inhibited growth. Further experiments are now recorded with antagonists of folic acid administered by intraperitoneal injection or in the food to chickens which had

been inoculated with Rous sarcoma as described in the preceding paper (Abstract 2328).

The development of Rous sarcoma was inhibited by 4-amino-pteroylaspartic acid and by 4-amino-pteroyl-D(-)glutamic acid. Toxic effects were pronounced when intraperitoneal injections were given to 2-day-old chicks; 8-day-old chicks were more tolerant. Day-old chicks tolerated 4-amino-pteroyl-D(-)glutamic acid in the food, in quantities of 80 mg. per kilo of food, without toxic effects. The 4-amino-pteroylglutamic acid killed baby chicks but was well tolerated by adult fowls. The toxicity and tumour-inhibiting properties of 4-amino-N-methyl-pteroylglutamic acid appeared to resemble those of 4-amino-pteroyl-D(-)glutamic acid. The toxicity appeared to be due solely to the severity of the vitamin deficiency resulting from too intensive treatment. Oral administration was the method of choice, since tumour growth could be inhibited in a greater percentage of the fowls without toxic effects. Evidently Rous sarcomata were more directly dependent for their growth on the dietary folic acid than were normal tissues of the chicks which did not develop severe vitamin deficiency in the time required to demonstrate inhibition of tumour growth by diets free from folic acid. It was possible that the chicks were protected by stores of the vitamin which were not available to the tumours. If this be true, the most desirable method of treatment would be the administration, in the diet, of chemicals which would antagonize the vitamin present in the food. It was shown that 4-amino-pteroylaspartic acid and 4-amino-pteroyl-D(-)glutamic acid produced this result. *L. Foulds*

2330. **Mammary Carcinoma in Female Rats Fed 2-Acetylaminofluorene**
R. W. ENGEL and D. H. COPELAND. *Science* [*Science*] **108**, 336–337, Sept. 24, 1948. 7 refs.

Twenty-five piebald female rats received a semi-purified diet containing 0·03% 2-acetylaminofluorene from the age of 23 days, when they weighed 25 to 50 mg. The rats were caged individually. They attained a weight of 200 g. in about 16 weeks, compared with 6 to 8 weeks for rats on a similar diet without acetylaminofluorene. One rat died tumour-free after 86 days. The remaining rats all developed mammary carcinoma after receiving acetylaminofluorene for 95 to 165 days. Previous investigators have recorded incidences of mammary tumours up to 75% in rats fed with 2-acetylaminofluorene, but apparently an incidence of 100% has not been attained before. It is not yet determined whether age or strain of rat or type of diet accounts for the result. *L. Foulds*

2331. **Attempt at Malignant Transformation of Connective Tissue of Mice *in vitro*.** (Опыт малигнизации соединительной ткани мыши ***in vitro***)
S. V. BENEVOLENSKAYA. Архив Патологии [*Arkh. Patol.*] **10**, No. 5, 7–10, Sept.–Oct., 1948. 5 figs., 10 refs.

Fragments of muscle and connective tissue of newborn Strong A high-breast-cancer strain mice were grown in Carrel flasks on a medium, whose solid part consisted of 8 drops of fowl plasma, 8 drops of Tyrode solution and 4 drops of chick-embryo extract and liquid part of 12 drops of Tyrode solution and 8 drops of horse serum. The liquid part of the medium was changed every 5 to 6 days. The tissues, which were transferred to fresh medium every 15 to 20 days, were divided into treated and control groups. Methylcholanthrene in horse serum was added to the first group of tissue after the second passage to give a final concentration of 1 in 1,250,000 in the medium. The same procedure was repeated at each change of the liquid part of the medium, or after each passage during 5 to 6 consecutive transfers of tissue on to the fresh medium.

After 5 to 6 passages, the cultures were grown on medium without methylcholanthrene. Forty days after the transfer from medium to which methylcholanthrene was added, changes were observed in the rate of growth and in the morphology of the treated cultures when compared with the control cultures. The cells in treated cultures grew more rapidly while the cells in control cultures grew more slowly and finally ceased to grow after 170 days. In cells of treated cultures polygonal forms and anisocytosis were seen, and they conglomerated especially at the periphery of the zone of growth. Multinucleated cells were also frequently observed. In general, the appearance of the treated cultures resembled that of sarcomata grown *in vitro*.

The treated cultures, after growth for 3 months on carcinogen-free media, were transplated subcutaneously into four 2-month-old Strong A mice. Each mouse received 2 to 3 cultures. After 1½ months, 1 of the mice developed a tumour which on histological examination was found to be a sarcoma. This tumour was successfully transplanted into other mice of Strong A strain. The author considers that the possibility that milk factor is involved in the malignant transformation of the connective tissue of Strong A high-cancer strain mice grown *in vitro* cannot be excluded. Experiments are in progress with similarly treated tissues of C57 low-breast-cancer strain mice grown *in vitro*, in an attempt to elucidate the part played by the milk factor in the observed malignant transformation of connective tissue cells. *L. Dmochowski*

2332. **Morphology of Phosphorus Metabolism in Normal and Pathological Conditions.** (Морфология фосфорного обмена в норме и патологии)
A. G. ANDRES and L. V. SHERSHULSKAYA. Архив Патологии [*Arkh. Patol.*] **10**, No. 5, 11–23, Sept.–Oct., 1948. 11 figs., 14 refs.

Mice, which were employed in the experiments, were divided into three groups. The first group of animals received once a week 2 drops of a 0·5% solution of methylcholanthrene in benzene on the same place on the skin of the back. The second group of mice received in addition subcutaneous injections of 0·015 c.c. of Bogomoletz's antireticular cytotoxic serum, and the third group 0·0005 c.c. doses of serum. The titre of the serum was 1 in 250 and the injections, started on the thirteenth day of the experiment, were given every third day. An interval of 14 days followed each course of 3 injections. As no appreciable differences in the number of tumours

and in the time of the appearance of tumours were observed in mice of the three groups, all mice were grouped together for the study of alkaline and acid phosphatase during the induction of malignant changes in the skin by methylcholanthrene. Parts of untreated skin served as controls.

For the demonstration of alkaline phosphatase Biesele's modification of Gomori's method was used, and for the demonstration of acid phosphatase the method of Wolf, Kabat, and Newman was employed. Material for histological studies was taken from mice killed 12 hours, and 1, 2, 4, and 7 days after the first application of the carcinogen, from mice killed 1 and 7 days after the second application of methylcholanthrene, and after 7 days from mice which had received from 3 to 20 applications of the carcinogen. Material from 67 mice was examined.

Alkaline phosphatase was observed in the skin of mice 24 hours after the first application of the carcinogen, mainly in the subcutis. Foci of inflammation and of epithelial hypertrophy contained a fair amount of alkaline phosphatase and benign papillomata hardly any, but it was present in considerable amounts in papillomata with signs of malignancy. Non-keratinizing basal carcinomata contained some alkaline phosphatase and none was found in the keratinizing tumours. Spindle-cell sarcomata contained only small quantities of alkaline phosphatase.

Acid phosphatase was not found in normal skin. It was present in malignant tumours, like alkaline phosphatase, in the subcutis, but unlike the latter it was also found in great amounts in the basal layer of the epidermis and in the stratum granulosum, and in other layers it stained rather diffusely. Acid phosphatase was present in both keratinizing and non-keratinizing types of carcinomata and also in spindle-cell sarcomata.

The location of alkaline phosphatase differed therefore to a certain extent from that of acid phosphatase. The latter was only found in the skin of mice killed 48 hours or more after the first application of the carcinogen, while the former was detected already after 24 hours. All layers of hyperplastic epithelium contained alkaline phosphatase after the sixth application of methylcholanthrene, while acid phosphatase was not found until after the eighth application of the carcinogen. *L. Dmochowski*

2333. **Experimental Tumours of Rabbit Uterus due to the Action of Methylcholanthrene.** (Экспериментальные опухоли кролика при действии метилхолантрена)

A. M. TROITSKAYA-ANDREEVA. Архив Патологии [*Arkh. Patol.*] **10**, No. 5, 23–26, Sept.–Oct., 1948. 34 refs.

Experiments carried out on 50 female rabbits during the years 1938–41 are described. Each of the rabbits received a single injection of varying quantities—from 2·0 to 15·0 mg.—of methylcholanthrene in vaseline oil into the left horn of the uterus. After the injection, the horn of the uterus was ligated. Three tumours developed at the sites of injection. One tumour, an adenoma, was discovered 1,005 days after the injection of 5·0 mg. of the carcinogen. The remaining two tumours, both sarcomata, developed 1,083 and 1,106 days after the injection of 10·0 and 5·0 mg. of methylcholanthrene respectively. These two tumours gave rise to metastases in the peritoneal cavity and in the lungs. The adenoma is described as a spontaneous tumour because of previously recorded spontaneous tumours of the same type in rabbits. The two sarcomata, however, which appeared nearly 3 years after the injection of the carcinogen, are described as induced tumours. Histological examination of the uteri of the rabbits, which died or were killed, showed no signs of proliferation of the cylindrical epithelium, despite the long duration of the experiment. *L. Dmochowski*

CLINICAL PATHOLOGY

2334. **Cold Agglutinins in Normal and Pathological Conditions. Their Value in Clinical Practice.** (Hemoaglutininas a frigore en terrenos normales y patológicos. Su valor en clínica)

H. VACCARO, L. PAREDES, and C. PAREDES. *Revista Médica de Chile* [*Rev. méd. Chile*] **76**, 548–559, Sept., 1948. 44 refs.

The authors give a résumé of the most important work done on agglutinins in atypical pneumonia and haemolytic anaemias. Their own study comprises research into cold agglutinins, both auto-agglutinins and iso-agglutinins, with group O erythrocytes. The 2,000 individuals examined were either normal or suffering from pneumonia, haemolytic anaemia, or various other clinical states; women during pregnancy and the puerperium were also included. Of the total examined, cold agglutinins were demonstrated in 9·4%, and of these 77·1% had a very low titre and 22·9% a higher one. Of 300 normal sera 13 were positive but with only very low titres. The higher titres were found in cases of atypical pneumonia, haemolytic anaemia, Raynaud's disease, and cirrhosis of the liver. All cases of atypical pneumonia were positive, and the authors stress the importance of repeated estimation to discover a rising titre. Of cases of haemolytic anaemia 36·6% were positive; and in 1 case of paroxysmal haemoglobinuria the titre was 1 in 2,048. Findings were positive in only 5% of pregnant women. *Paul B. Woolley*

2335. **An Evaluation of the Thymol Turbidity Test**

R. G. ERNST and L. B. DOTTI. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 316–329, Sept., 1948. 3 figs., 13 refs.

The thymol turbidity test, a slight change being made in the Shank and Hoagland modification of Maclagan's original technique (*J. biol. Chem.*, 1946, **162**, 133), was carried out on: (1) 500 normal patients. (2) 527 patients suffering from diseases other than diseases of the liver; and (3) 124 patients with disease of the liver or biliary tract. From a study of (1) it was decided that the normal range for the test was 0·0 to 5·0 units. In (2) most results fell within the limits of normality, although in a few diseases (listed in a table) thymol

turbidity values were raised. From (3) it was found that in cases of definite parenchymatous damage to the liver (especially infective hepatitis) thymol turbidity values were markedly raised, successive records forming a useful guide to the progress of the disease. "Compensated" cirrhosis and cholelithiasis often give equivocal results, which probably depend again on the degree of parenchymatous damage. It is pointed out that specimens should be taken with the patient fasting and that, although refrigeration does not alter the accuracy of the results, heating the sera at 56° C. for 30 minutes will lower the readings sufficiently to render them inaccurate.

The cephalin-cholesterol flocculation test described by Hanger, with the modification introduced by Neefe and Rheinhold (*Science*, 1944, **100**, 83) was carried out on as many patients as possible for whom thymol-turbidity values were known. It was found that in groups (1) and (2) the Hanger test was probably more accurate, while in the presence of liver disease the results of the two tests were parallel. *J. B. Wilson*

2336. **Studies of Erythrocyte Counting. I. Technical Errors.** [In English]
H. F. LANGE and H. PALMER. *Acta Medica Scandinavica* [*Acta med. scand.*] **131**, 451–465, Oct. 15, 1948. 2 figs., 3 refs.

The authors have studied possible technical errors in their method of red cell determination, and find by physical measurements a variation in the height of the Buerker counting chambers of +3·5 to +8%, with the same cover-glass. They note a variation between the counts made on the two fields of the same slide, and an unequal distribution of the cells in the counting chamber with a tendency to increase towards the inner part of the field. This irregularity is not related to the erythrocyte sedimentation rate, the diluting fluid, or the time of mixing. They prefer to use a counting chamber without clamping the cover-glass, to ensure that Newton's rings are of the same order on each side. They advise a diagonal counting of the squares and the use of 0·9% solution of sodium chloride as a diluting fluid rather than Hayem's fluid, although they recognize that microbic pollution will soon render it unusable. *E. T. Ruston*

2337. **Studies of Erythrocyte Counting. II. Technical-physiological Errors.** [In English]
H. F. LANGE and H. PALMER. *Acta Medica Scandinavica* [*Acta med. scand.*] **131**, 555–564, Oct. 30, 1948. 4 figs.

Blood obtained at 2-minute intervals by venipuncture without tourniquet had an almost constant erythrocyte content, and was therefore taken as the standard for the measurement of all variations resulting from adoption of other techniques of blood collection. Rendering the skin at the puncture site hyperaemic by rubbing with ether-soaked cotton wool caused a 5% reduction in the erythrocyte content, attributed to dilution with tissue fluid. Use of a "scarificator" caused an average deviation of 3%, and of a knife only 1·9%. Pressure in order to force the blood out caused an average rise of 7·5% in the erythrocyte content; in one instance great pressure caused a rise of 26%. Wiping away the first drop of blood caused a mean deviation of 2·5%, but allowing it to run away only one of 1·8%. With blood from the finger pulp there was a deviation of 0·5% to 4·8%, but with blood from the ear lobe the deviation was 1·5% to 7·6%. The former therefore approximates more closely to venous blood, and is also less subject to fluctuation in erythrocyte content. Half a minute should elapse before blood is drawn into the pipette, otherwise there is greater variation. *Bernard Freedman*

2338. **Studies in Serum Proteins. IV. Clinical Studies Employing Rapid Chemical Fractionation Procedures, with Particular Reference to the Frequency and Significance of Hypoalbuminemia**
W. Q. WOLFSON, C. COHN, E. CALVARY, and E. M. THOMAS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1276–1288, Oct., 1948. 2 figs., 36 refs.

It is recognized that the Howe sodium sulphate fractionation method gives high values for serum albumin because some α-globulin is included. The authors have devised a new chemical fractionation method (full details of which will be published in *Amer. J. clin. Path.*) which they have applied to 500 sera, obtaining results approximating to those of an electrophoretic analysis.

Hypoalbuminaemia was present in 34 patients, who had a serum albumin concentration below 2 g. per 100 ml.; in 10 (all with the nephrotic syndrome) the level fell below 1 g. This series included 18 cases of chronic glomerulonephritis, 3 cases of hepatic cirrhosis, 3 cases of multiple myelomata, 2 cases of renal amyloidosis secondary to tuberculosis, and 2 cases of gastro-intestinal carcinoma, as well as cases of Hodgkin's disease, dermatomyositis, rheumatic fever, and idiopathic lymphatic atrophy. An increase in serum β-globulin and a decrease in γ-globulin was observed in 16 nephrotic children. A greater increase in total serum globulin, β-globulin, and γ-globulin was found in patients with reticulo-endothelial involvement and hepatic dysfunction. Hypoalbuminaemia occurring in this last group may be due to involvement by disease processes of the globulin-forming organs. *E. T. Ruston*

2339. **On Serum Copper in Angina Simplex and in Infectious Mononucleosis.** [In English]
S. MUNCH-PETERSEN. *Acta Medica Scandinavica* [*Acta med. scand.*] **131**, 588–596, Oct. 30, 1948. 1 fig., 5 refs.

The copper levels in serum in 50 normal men and 50 normal women, estimated by a modification of the sodium diethylcarbamate method, were found to be 108 and 118 μg. per 100 ml. respectively. Similar estimations were made on 22 patients with different forms of non-specific sore throat (angina simplex) and 10 patients with infective mononucleosis. All the subjects chosen were over 15 years of age, because the normal copper level in the serum of children under 14 was found to be appreciably higher than that in adults. The diagnosis was established by the presence of pharyngitis, a differential

blood count, and, in all but 2 of the cases with mononucleosis, a Paul–Bunnell reaction. From 2 to 6 estimations of copper in serum, erythrocyte sedimentation rate, and differential blood count were made on each patient. The average of the first two values obtained showed that a considerable rise in the copper level occurred early in the illness in both groups, the increase being greater in infective mononucleosis than in angina simplex. The average values in the former were 190 and 206 μg. per 100 ml., and in the latter 151 and 168 μg. per 100 ml., for males and females respectively. That the rise in copper level in angina simplex occurred almost entirely in the serum was shown by estimating in a few cases the copper content of the centrifuged erythrocytes; this was only slightly raised above the normal value. No explanation is offered for these observations, which the author claims to be original. *Wilfrid E. Hunt*

2340. **Normal and Pathological Lymphadenogram in the Light of Own Research.** [In English]
T. TEMPKA and M. KUBICZEK. *Acta Medica Scandinavica* [*Acta med. scand.*] **131**, 434–450, Oct. 15, 1948. 18 figs., 13 refs.

This is a report of three years' work done at Cracow before the last war. Smears were made from the material aspirated by a " dry-sterilized " syringe and needle—an operation which rarely required a local analgesic—and stained by Pappenheim's method. From their study of normal material—lymph nodes exposed in the foramen ovale during operations for the repair of femoral herniae —the authors were able to differentiate lymphocytes from reticular cells against a background of amorphous debris. They bring forward evidence of lymphocytic phagocytosis by the reticular cells and destruction of degenerate basophilic red cells. Their pathological material included 32 cases of lymphadenoma, 18 cases of tuberculosis, 13 cases of leukaemia, and 7 cases of metastatic growth. They were unable to recognize giant cells or tubercle bacilli in any of the tuberculous cases, and found typical Sternberg cells in only 7 cases of Hodgkin's disease. The authors point out that a myeloid metaplasia can occur in lymph nodes apart from leukaemia, and claim that their method, although simple, will support only a clinical diagnosis. [It would surely be preferable to excise the enlarged lymph node for a fuller histological examination.] *E. T. Ruston*

2341. **Glucose Tolerance: II. Evaluation of Glucose Tolerance in Liver Disease and Comparison of the Relative Value of Three Types of Tolerance Tests**
J. MOYER and C. WOMACK. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 446–457, Oct., 1948. 45 refs.

The authors carried out: (*a*) the one-dose standard glucose tolerance test; (*b*) the one-hour, 2-dose Exton Rose test; (*c*) the intravenous glucose tolerance test on 19 cases of cirrhosis of liver and on 10 cases of infective hepatitis in various stages of convalescence. Diagnosis was confirmed by liver biopsy in every case. To determine the importance of these tests in liver disease the authors compared the results with those of the following liver function tests: bromsulphalein retention, icterus index, cephalin flocculation, thymol turbidity, prothrombin time determination, and estimation of albumin–globulin ratio.

In 7 cases of cirrhosis of the liver there was a typical diabetic curve and, although the diagnosis was confirmed by liver biopsy, the authors state that absolute proof that these were not cases of insulin insufficiency is lacking. In the remaining 22 patients the curve was either normal or flat or oxyhyperglycaemic (lag storage). From their observations the authors conclude that glucose tolerance tests are of no value in differential diagnosis of jaundice, but for assessment of liver function in diseases of the liver they compare favourably with other liver function tests. Of the three, the standard glucose tolerance test is regarded as most useful.

[Critical study of the blood sugar levels during the three types of glucose tolerance test shows that these tests have very little, if any, value in liver dysfunction.]
S. Karani

MORBID ANATOMY

2342. **Pulmonary Adenomatosis. A Report of Three Cases**
G. W. DRYMALSKI, J. R. THOMPSON, and H. C. SWEANY. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 1083–1093, Sept., 1948. 6 figs., 26 refs.

Pulmonary adenomatosis accounts for about 5% of all pulmonary tumours and probably results from non-specific irritation. Occurring in the sixth decade, and more commonly in women than in men, the disease runs a course varying from weeks to 2 years and is without distinctive clinical or radiological features, although it may simulate tuberculosis, carcinoma, or pneumonia. Macroscopically the lung resembles that of grey hepatization, while microscopically the alveolar walls are lined by uniform non-ciliated cubical or columnar cells, which may assume papillary formations and which are probably of bronchiolar origin. Mitoses are infrequent. The disease is considered to be a benign variant of the so-called alveolar-cell carcinoma, and has many features in common with pulmonary adenomatosis in sheep (Jaagsiekte).

Of the cases reported here, one shows a small focus of malignant change in the adenomatous cells and another is the second surgical specimen of the condition to be recorded. *R. C. B. Pugh*

2343. **Arthritis Deformans of the Hip Joint and its Pathological Histology. Research in Polarized Light**
P. E. LUGIATO. *Journal of Bone and Joint Surgery* [*J. Bone Jt Surg.*] **30A**, 895–902, Oct., 1948. 11 figs., 6 refs.

The pattern of the collagenous fibrils of articular cartilage has been studied in unstained sections from osteo-arthritic joints by means of polarized light. Disturbance of the normal fibril system is one of the first manifestations of cartilage degeneration, and various appearances of the fibrillar structure, both of cartilage

and of bone, are described in the different stages of the disease.

[No new conclusions are reached; the technique is not, of course, new, and many others have also failed to obtain much helpful information by its use.]

Douglas H. Collins

2344. **Trilocular Heart with Bilateral Aneurysmal Dilatation of the Pulmonary Arteries**

G. J. CUNNINGHAM. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 379–386, July, 1948. 3 figs., 15 refs.

The case reported is an example of complete agenesis of the interatrial septum with absence of the pars membranacea. The anterior mitral flap was fused with the medial tricuspid flap and firmly adherent to the upper margin of the interventricular septum, but the resultant structure was centrally deficient. In addition to the gross cardiac defect there was massive thrombosis in the aneurysmal pulmonary arteries, much of which was estimated to be many months old. The patient was 51 at death and had been under constant observation for 20 years. *A. C. Lendrum*

2345. **Ebstein's Anomaly of the Tricuspid Valve**

K. WALTON and A. G. SPENCER. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 387–393, July, 1948. 5 figs., 15 refs.

The lesion described by Ebstein—a malformation of the tricuspid valve with " displacement downward " into the ventricle, the flaps taking origin in part from the ventricular wall—has previously been reported 18 times; in 2 of these cases the defect was associated with a closed foramen ovale. There is no standard clinical picture, as the degree of incompetence and the amount of interauricular shunt vary from case to case. In the present case the patient, a woman of 53 years, had been healthy till an accident one year before. Cardiac failure was followed by popliteal thrombosis and pulmonary embolism. Necropsy revealed an ischaemic fibrosis of the left ventricular apical and septal myocardium in addition to the Ebstein anomaly; paradoxical femoral embolism was also found. *A. C. Lendrum*

2346. **Diffuse Angiectasis of the Cerebral Meninges of the Newborn Infant. Report of Three Cases**

E. L. POTTER. *Archives of Pathology* [*Arch. Path.*] **46**, 87–96, Aug., 1948. 6 figs., 1 ref.

This work is reported from the University of Chicago and the Chicago Lying-in Hospital. Diffuse angiectasis has already been described in the meningeal area exposed at operation. In the cases reported the entire leptomeninges of the cerebrum and cerebellum were involved. There was a great increase in the number and size of the meningeal vessels, which were very tortuous and formed a scroll-like pattern. These vessels had the structure of capillaries and terminal veins. In all cases the brain itself and the pachymeninges were both macroscopically and microscopically normal. Each infant had an enlarged heart and in the two cases in which it is mentioned the thyroid size was increased. One infant also had an increased number of subcapsular veins of the liver and dilatation of the centrilobular veins. One infant died during labour; two survived 25 and 32 hours respectively, and both appear to have been cyanotic and to have had respiratory difficulties. *Peter Harvey*

2347. **Significance of Agonal Changes in the Human Liver**

H. POPPER. *Archives of Pathology* [*Arch. Path.*] **46**, 132–144, Aug., 1948. 3 figs., 24 refs.

The material for this study of the agonal changes in the liver at Cook County Hospital and the North Western University Medical School, Chicago, consisted of: (1) 226 needle biopsy specimens from 156 cases and 108 specimens obtained by surgical excision at laparotomy, some of which were fairly normal. (2) Biopsy and necropsy material available from the same patient in 38 cases. In 4 of these the interval after death was less than 48 hours. (3) Necropsy material from 351 males in the armed forces all under 45 years and all of whom had died by accident or illness within 24 hours: (*a*) 96 cases of instantaneous death; (*b*) 255 cases in which death had occurred within 24 hours. The material was fixed in a variety of fluids, mainly Carnoy solution. Paraffin sections were used.

Cytoplasmic changes due to the absence of glycogen were seen in necropsy material. Dissociation of the liver cell cords with isolation of individual liver cells may be the result of agonal or necropsy change, and so regurgitation jaundice cannot be explained by communication between the bile capillaries and the perisinusoidal spaces, which result from this dissociation. In life the perisinusoidal spaces are almost completely obliterated, but in the agonal period these spaces open up revealing reticulin connecting the walls of the sinusoids with the parenchyma cells. Consequently in cases of instantaneous death, these perisinusoidal spaces usually remain closed. This point was confirmed by animal experiments and might be of medico-legal significance.

Peter Harvey

2348. **The Pancreas in Uremia: A Histopathologic Study**

A. H. BAGGENSTOSS. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 1003–1017, Sept., 1948. 3 figs., 10 refs.

In about 45% of 270 cases of uraemia the pancreas was found at necropsy to contain a variable number of acini which were dilated by inspissated secretion and lined by a degenerate epithelium. This condition may be due to thickening of secretion by dehydration or impairment of the secretin hormone mechanism. It was found in moderate degree in 40 of 200 control cases. The most common cause of death in the 40 control cases was intestinal obstruction. The condition is of interest in connexion with fibrocystic disease of the pancreas in childhood. *D. M. Pryce*

Microbiology

VIRUSES

2349. **Influenza Virus Infection in the Hamster. A Study of Inapparent Virus Infection and Virus Adaptation**
W. F. FRIEDEWALD and E. W. HOOK. *Journal of Experimental Medicine* [*J. exp. Med.*] **88**, 343–353, Sept. 1, 1948. 1 fig., 12 refs.

The usual response of the hamster to intranasally introduced influenza virus is the production of antibodies without lung lesions. This serological response has been used to detect influenza virus in throat washings.

The authors have now adapted two strains of the A virus and one B strain to the hamster by serial intranasal passage of lung suspension at 4-day intervals. With the A strains, Ga 47 and PR 8, between the first and sixth passages no lung lesions were noted although virus multiplication could be detected by sub-inoculation into eggs and mice and by complement fixation. At the seventh passage there was a sudden increase in the virulence of both strains, coupled with a much higher virus titre and the appearance of agglutinins for human erythrocytes and to a lower titre for guinea-pig cells. When the suspensions were incubated at 37° C. for 6 hours the presence of some agglutinin for fowl cells could also be demonstrated. The increase in virulence continued irregularly up to the eleventh passage when free agglutinins for fowl cells first appeared and the virus titre was as high as in the parent strain. The temperature response to adapted and non-adapted strains is shown in charts.

The response to the Lee strain of influenza B virus was quite different. Lung lesions and fatalities were encountered in the first passage as well as substantial amounts of virus, specific complement-fixing antigen, and agglutinins for fowl, guinea-pig, and human erythrocytes. There was no increase in virulence with passage, and the level of infectivity and virulence remained lower than with the adapted A strains. *A. P. Goffe*

2350. **Mucins and Mucoids in Relation to Influenza Virus Action. I. Inactivation by RDE and by Viruses of the Influenza Group, of the Serum Inhibitor of Haemagglutination**
S. G. ANDERSON. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 347–354, Sept., 1948. 12 refs.

Francis (*J. exp. Med.*, 1947, **85**, 1) showed that there is present in normal mammalian sera a substance (now generally known as the Francis inhibitor) which will inhibit the agglutination of red cells by influenza viruses. It is detected by ascertaining the highest dilution of serum which will inhibit agglutination of fowl red cells by Lee (influenza B) virus previously heated at 55° C. for 30 minutes.

This first paper in the series details experiments which show that the inhibitor in human serum is inactivated by the receptor-destroying enzyme or mucinase secreted by *Vibrio cholerae* in the form either of filtrates previously heated at 55° C. in the presence of calcium, or of eluates from washed red cells on to which the enzyme had been adsorbed in the cold. The inhibitor is also inactivated if incubated at 37° C. with active influenza virus (strains of Lee, MIL B, and swine virus, and to a lesser extent by the Melbourne and WSE strains of influenza A). It is therefore postulated that some strains of influenza virus secrete a mucinase and that the Francis inhibitor is a mucin. Very similar results have recently been reported by Hirst (*J. exp. Med.*, 1948, **87**, 301). *R. Hare*

2351. **Mucins and Mucoids in Relation to Influenza Virus Action. II. Isolation and Characterization of the Serum Mucoid Inhibitor of Heated Influenza Virus**
J. F. MCCREA. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 355–370, Sept., 1948. 5 figs., 25 refs.

This paper is an account of further work on the Francis inhibitor, and deals with attempts to purify it and identify the substances responsible. Preliminary studies showed that it was almost completely precipitated by 50% saturation with ammonium sulphate or by 30% methanol–water mixtures. Seromucoid prepared by Rimington's method (*Biochem. J.* 1940, **34**, 931) contained, in relation to its nitrogen content, a high proportion of the inhibitor. The inhibitor is also inactivated by crystalline trypsin, chymotrypsin, pepsin, and cyanide-activated papain, but not by crystalline ribose nuclease or testicular hyaluronidase. These findings suggest that the substance in question contains protein, while the further observation that it is also destroyed by potassium periodate suggests that a carbohydrate is also present. For these reasons the substance is probably a mucin. Similar conclusions have been reached by Hirst (*J. exp. Med.*, 1948, **87**, 301). *R. Hare*

2352. **Mucins and Mucoids in Relation to Influenza Virus Action. III. Inhibition of Virus Haemagglutination by Glandular Mucins**
F. M. BURNET. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 371–379, Sept., 1948. 14 refs.

Study of the Francis inhibitor present in normal mammalian sera has shown that it is destroyed by the mucinase secreted by *Vibrio cholerae* or by the virus itself (Anderson, *Aust. J. exp. Biol. med. Sci.*, 1948, **26**, 347; Hirst, *J. exp. Med.*, 1948, **87**, 301), while further work by Hirst in the same paper and by McCrea (*Aust. J. exp. Biol. med. Sci.*, 1948, **26**, 355) has shown that it is destroyed by proteolytic enzymes and by potassium

periodate. This suggests that the substance in question is a mucin and probably identical with the receptor substances present on red cells and tissue cells. In the present investigation the author employed suspensions of various mucoid substances and showed that they behave in much the same way as the Francis inhibitor. The substances in question comprised mucin from ovarian cysts, the purified mucoids of groups A and O red cells, and mucoid material from pseudomucinous cysts. The preparation of these substances is described in detail. Suspensions of all of them inhibited agglutination of red cells by influenza virus, and particularly by virus whose own mucinase had been inactivated by previous heating. Their inhibitory powers were much reduced if the suspensions were previously treated with potassium periodate, with the receptor-destroying enzyme (or mucinase) secreted by *V. cholerae*, or with that secreted by the virus itself. It is therefore probable that the receptors in the cells, the Francis inhibitor in the serum, and mucoid substances of human origin all behave in much the same way when placed in contact with influenza virus, forming a virus–mucin complex which can be rapidly broken down by means of mucinases secreted by the virus particles themselves. *R. Hare*

2353. **Mucins and Mucoids in Relation to Influenza Virus Action. IV. Inhibition by Purified Mucoid of Infection and Haemagglutination with the Virus Strain WSE**
F. M. Burnet. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 381–387, Sept., 1948. 3 figs., 3 refs.

Strain WSE is a derivative by chorio-allantoic passage of the standard WS strain of influenza A, and in the author's experience it is abnormal in that it is the only strain of influenza A whose ability, while in the unheated active state, to agglutinate red cells can be inhibited in high titre by mucins. It was therefore important to determine whether the presence of mucoid substances could inhibit infection with this strain. This was shown to be the case with both mice and eggs. An additional observation was that treatment of the mucoid with small amounts of periodate increased its inhibitory action both for haemagglutination by this strain and its infectivity for the allantoic cavity of embryonated eggs. *R. Hare*

2354. **Mucins and Mucoids in Relation to Influenza Virus Action. V. The Destruction of "Francis Inhibitor" Activity in a Purified Mucoid by Virus Action**
F. M. Burnet. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 389–402, Sept., 1948. 10 figs., 10 refs.

Purified mucoid was obtained from two ovarian cysts by a somewhat elaborate process the main steps of which comprise preliminary removal of unwanted material by treatment with acetic acid at *p*H 4·5 and heating at 100° C., precipitation with ethanol, and drying *in vacuo*. Further treatment with 90% phenol yielded a white powder which produced an opalescent and slightly viscous solution in distilled water.

It has already been postulated that active unheated virus secretes a mucinase which inactivates the mucoid receptors on red cells and tissue cells, and the present paper consists for the most part of a study of this enzyme action, the purified mucin being used as a substrate. With virus such as the Lee strain of influenza B, which appears to secrete the most powerful enzyme, the inactivation of the mucoid followed an approximately logarithmic course. With less active viruses (WSE, Melbourne, and IAN-O) the inactivation proceeded only to a certain level, owing, in the opinion of the author, to "exhaustion of that portion of the substrate susceptible to the action of the virus concerned". It is also interesting to note that the O and D phases of influenza A strain BEL behaved alike.

Inactivation reaches its highest level at a *p*H of 6·2 and falls off rapidly below *p*H 5·7 or above *p*H 7·0. It is more complete in the presence of free calcium ions and at 36° C. and at 0° C. The receptor substance isolated direct from red cells by Bovarnick and de Burgh (*Science*, 1947, **105**, 550) behaves in much the same way as the purified mucoid. *R. Hare*

2355. **Mucins and Mucoids in Relation to Influenza Virus Action. VI. General Discussion**
S. G. Anderson, F. M. Burnet, S. Fazekas de St. Groth, J. F. McCrea, and J. D. Stone. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 403–411, Sept., 1948. 20 refs.

This paper summarizes the preceding five articles and gives a detailed exposition of the views of the Australian school of virus workers on the mechanism of the virus–host-cell relationship as exemplified by influenza virus. In brief, it is postulated that influenza viruses can be adsorbed by a variety of receptors whose common denominator is the presence of mucopolysaccharide. Substances of this nature are probably present on the surface of red cells, on the cells of the pulmonary epithelium, and on those lining the chorio-allantoic cavity of the developing egg. Virus particles in the neighbourhood of such cells are therefore quickly adsorbed on to their surfaces. Substances of this nature are, however, also present in the serum of normal mammals (constituting the so-called Francis inhibitor), in normal allantoic fluid (Hardy and Horsfall, *J. exp. Med.*, 1948, **88**, 463), and in the mucins of the epithelial surfaces as well as those in various forms of ovarian cyst. If these different kinds of mucin are present in suspension along with influenza virus, a complex is formed of such a nature that, if cells are then added to the mixture which have mucin receptors on their surface, they fail to adsorb the virus. The mucin in suspension therefore competes, and apparently very successfully, for that part of the virus surface which normally attaches itself to the mucin receptors on susceptible cells.

Influenza viruses carry enzymes as part of their surface structure, which can react with these mucoid substances and inactivate them. In this respect the enzymes are evidently of the same nature as the mucinases secreted by certain strains of *Vibrio cholerae*. There is marked correspondence between the action of the virus enzymes and

the receptor-destroying enzyme of *V. cholerae* filtrates—a fact already noted by Stone (*Aust. J. exp. Biol. med. Sci.*, 1947, **25**, 137), and further amplified in the present series of papers. Thus, the enzymic activity of both receptor-destroying enzyme and Lee virus is dependent on the presence of calcium ions, and the optimum *p*H (6.2) is about the same. The conditions of thermal inactivation of both the receptor-destroying enzyme and the virus enzymes also point to a basic similarity. In the absence of Ca ions, and in an alkaline medium, the enzymes in both cases are inactivated at lower temperatures than in the presence of Ca ions or at a *p*H below 7.0.

These observations are important because they provide a clue to the mechanism by which the virus reaches the interior of suceptible cells. The first step would appear to be the adsorption of the virus by mucoid receptors on the surface of these cells. This having been accomplished, the virus particles themselves then produce enzymes which inactivate these mucoid receptors and in so doing liberate the adsorbed virus particles. Some are probably liberated outside the cells, but it is postulated that a proportion are liberated inside the cell itself, thus providing for the virus that *milieu* which is necessary for its multiplication. *R. Hare*

2356. **Antigenic Differences Among Influenza A Viruses, Including Serologic Response of Patients**
H. R. MORGAN, M. W. BARNES, and M. FINLAND. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1212–1219, Oct. 1948. 9 refs.

The serological response of 20 patients with clinical influenza during an epidemic at Boston in March–April, 1947, was analysed by comparing the rise in titre of antibody to four strains of influenza A, the swine influenza virus, and the Lee strain of influenza B. Three of the A strains—EB, GP, and DW—were isolated during the epidemic from 3 cases included in the study and the fourth was the classical PR 8 strain. Serum was collected before the third and after the tenth day of disease and pairs of specimens were examined together both by complement-fixation tests (CFT) with infected chorio-allantoic fluid as antigen and by the haemagglutination-inhibition (HI) technique. Seven pairs were tested by CFT and HI against all strains, and in the other cases tests against one or more strains were omitted.

The results can be summarized as follows. No significant response to Lee virus was found in any case. A positive response (4-fold or greater rise of titre) occurred to one or more of the A strains in all patients. The responses revealed by CFT and HI were frequently different, even when the same serum dilutions were tested against the same antigen in both tests on the same day. Individual cases showed unusual or low-grade responses to a majority of strains. A greater proportion of positive responses was obtained, and the mean increase in titre was higher, in CFT than in HI tests. The greatest proportion of positive responses and the highest mean increase of titre in both tests occurred with the PR 8 strain. The three freshly isolated strains, and especially the DW strain, provided poor antigens in HI tests.

Paired samples of serum from 6 cases were also tested by virus neutralization in the yolk sac against PR 8 virus, the three epidemic strains, and a fifth strain of A virus (FM_1) isolated at the same time during the epidemic in New Jersey. The patients included the three from whom the epidemic strains were isolated. None of the acute phase sera had any neutralizing titre for the local epidemic strains, while two had low titres for FM_1 and two had moderate titres and two low titres for PR 8. The highest rises in titre and highest titres in convalescence occurred with the PR 8 and FM_1 strains. A sporadic case in December, 1947, yielded a strain of influenza virus (PW); serum in this case failed to show any rise of antibody to PR 8 virus, swine virus, epidemic strains, or the strain from the patient's own throat.

The antigenic relations of the strains isolated from these cases to the classical PR 8, swine, and Weiss strains, and to three representative strains from the 1943–44 Boston outbreak were studied by preparing sera against each strain in the rabbit and carrying out cross-neutralization tests in the allantoic sac of chick embryos. The strains belonged to three main groups. The 1947 epidemic strains were inter-related and only slightly related to the 1943–44 strains, and showed no relation to PR 8 and Weiss virus. In this group the DW strain showed some differences from the others. The 1943–44 strains formed another group related to Weiss and PR 8 virus. The PW strain from the sporadic case at the end of 1947 showed no relation to the other strains.

[This is a most informative paper which repays close study by those interested in this field.] *A. P. Goffe*

2357. **Studies on the Relationship of Pteroylglutamic Acid to the Growth of Psittacosis Virus (Strain 6 BC)**
H. R. MORGAN. *Journal of Experimental Medicine* [*J. exp. Med.*] **88**, 285–294, Sept. 1, 1948. 17 refs.

The minimum dose of sodium sulphadiazine which will inhibit the growth of psittacosis virus was determined by inoculating various doses into the yolk sacs of fertile eggs on the sixth or seventh day of incubation and then giving 10,000 LD 50 of the 6BC strain of psittacosis virus by the same route. From 12 to 29 eggs were used for each dosage level, and the number surviving after 10 days was recorded. The minimum dose which would suppress the virus infection was 0·1 to 0·5 mg. A standard dose of 2·5 mg. was mixed with varying amounts of *p*-aminobenzoic acid or pteroylglutamic acid and inoculated similarly into eggs, followed by an inoculation of virus. Under these conditions both compounds opposed the inhibiting effect of sodium sulphadiazine and allowed the virus to multiply. On a basis of molarity *p*-aminobenzoic acid was three times as effective as pteroylglutamic acid. The activity of the latter was not due to breakdown into the former compound, since no *p*-aminobenzoic acid could be detected in the embryonic fluids up to 9 days after the injection of pteroylglutamic acid. The two compounds did not oppose the antiviral action of penicillin in a similar test. Two doses of *p*-aminobenzoic acid and pteroylglutamic acid, representing twice and ten times the minimum amounts opposing 2·5 mg. of sodium sulphadiazine, were tested against amounts of sodium sulphadiazine ranging from

0·5 to 50 mg. A direct relationship was found between the equivalent amounts of sodium sulphadiazine and *p*-aminobenzoic acid, showing that the antagonism is competitive, but an effective amount of pteroylglutamic acid could not be opposed by even 50 mg. of sodium sulphadiazine. The latter antagonism is thus non-competitive. Examination of the components of pteroylglutamic acid showed that glutamic acid was inactive while pteroic acid still showed competitive antagonism. Various analogues of pteroylglutamic acid were also tested. Pteroyldiglutamic acid, pteroyl-γ-diglutamic acid, and pteroyltriglutamic acid did not affect the growth of psittacosis virus, but antagonized the antiviral effect of sodium sulphadiazine. Pteroylaspartic acid was also an antagonist, but in larger doses.

The results are interpreted as showing that psittacosis virus requires *p*-aminobenzoic acid for the synthesis of pteroylglutamic acid, and that this effect is antagonized by sodium sulphadiazine. There is some indication that pteroylglutamic acid is synthesized by the virus itself, since it has been shown to be a dietary requirement for chickens and therefore probably cannot be synthesized by the embryo. *D. J. Bauer*

2358. **Acquired Resistance of Psittacosis Virus to Sulfadiazine and Effects of Chemical Antagonists on Sulfonamide Activity**

O. J. GOLUB. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1241–1248, Oct., 1948. 2 figs., 14 refs.

Sulphadiazine, when mixed with psittacosis virus 6BC and inoculated into eggs by the yolk-sac route, prolonged the life of the chick embryos. A quantity of 0·5 mg. of sulphadiazine was enough to protect for at least 10 days against $10^{4\cdot8}$ LD 50 of the virus. The surviving eggs contained considerable amounts of virus which could be recovered from the yolk sacs. The addition of 1 μg. of *p*-aminobenzoic acid to the inoculum antagonized the protective action of 1 mg. of sulphadiazine. Pteroylglutamic acid was less efficient, 0·1 mg. being required to show antagonism to 1 mg. of sulphadiazine. Pteroylglutamic acid alone had a slight stimulating effect on the growth of the virus.

Eggs inoculated with the virus of lymphogranuloma venereum were also protected by the addition of sulphadiazine, but this action was not antagonized by *p*-aminobenzoic acid. Ten passages of psittacosis virus 6BC in the presence of 0·5 mg. of sulphadiazine produced a strain which was resistant to sulphadiazine, sulphamerazine, and sulphathiazole. The resistance of the strain was unaltered by ten rapid yolk-sac passages in the absence of sulphadiazine. — *L. G. Goodwin*

2359. **The Effect of Certain Enzyme Inhibitors on the Activity and Growth of Psittacosis Virus**

T. E. BURNEY and O. J. GOLUB. *Journal of Immunology* [*J. Immunol.*] **60**, 213–221, Oct., 1948. 22 refs.

Iodoacetamide ($2\cdot5\times10^{-3}$ M), *o*-iodosobenzoate (10^{-4} M), *p*-chloromercuribenzoic acid (10^{-4} M), mercuric chloride (10^{-3} M), hydroquinone, proflavine, and mepacrine (all 10^{-3} M), when mixed with psittacosis virus *in vitro*, markedly reduce its capacity to grow in fertile eggs. As the first four substances all affect –SH groups, and the inhibition of the virus produced by *p*-chloromercuribenzoate is reversed by glutathione and cysteine, it is concluded that virus activity depends in part on enzyme systems involving –SH groups. The action of proflavine on the virus may be due to its inhibitory effect on adenine-containing enzyme systems; it is, however, not reversed by yeast nucleic acid. Mepacrine may affect virus multiplication by interfering with cytochrome reductase and glucose-6-phosphate dehydrogenase systems. Iodoacetic acid, 2-4-dinitrophenol, sodium fluoride, sodium azide, potassium cyanide, *p*-aminobenzoic acid, and urethane had no inhibitory effect on the virus. It is therefore likely that adenosine triphosphatase, enolase, catalase, and cytochrome oxidase systems are not essential to virus multiplication.

The observation that psittacosis virus will not grow in tissue culture after the medium has been exposed to *o*-iodosobenzoate or hydroquinone lends point to the warning that the effect of enzyme inhibitors may be as much on the host as on the parasite. *C. L. Oakley*

2360. **Effect *in vitro* of Specific Lipid Fractions of Animal Sera on Psittacosis Virus**

J. P. UTZ. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 186–189, Oct., 1948. 6 refs.

Following the finding by Casals and Olitsky (*Science*, 1947, **106**, 267) that some neurotropic viruses are inactivated after incubation at 37° C. with various animal sera, the present authors determined the effect of various fractions of chicken, rabbit, horse, sheep, and human sera on psittacosis virus. Different lipid fractions were employed to make tenfold dilutions of virus present in the allantoic fluid of chick embryos; the mixtures were held in contact at 37° C. for 1 hour and then inoculated intracranially (in doses of 0·03 ml.) into 6-week-old mice. Normal sera did not inactivate the virus, but lipid extracts of the same sera did have this effect; phospholipid-free and sphingomyelin–cerebroside fractions had a 10- to 100-fold inactivating effect, while the lecithin-like and cephalin-like fraction decreased the titre 10,000- to 100,000-fold. Comparable results were obtained with the "4" strain and with the 6BC and Gleason strains. Controls of water, saline, egg-yolk extracts, and commercial lecithin in concentration equal to that expected in serum extracts were all without inactivating effect. *R. Hare*

2361. **The Relationship of Varicella and Herpes Zoster: Electron Microscope Studies**

G. RAKE, H. BLANK, L. L. CORIELL, F. P. O. NAGLER, and T. F. M. SCOTT. *Journal of Bacteriology* [*J. Bact.*] **56**, 293–303, Sept., 1948. 17 figs., 13 refs.

Examination by the electron microscope of vesicle fluid from the lesions of various clinical types of herpes zoster has shown that the elementary bodies do not differ significantly in size or shape from those found in chicken-

pox. It would appear from the limited examples that the elementary bodies are most numerous in the early lesions; very large numbers were seen in a 12-hour specimen whereas in later specimens from the same case they were scanty. Fluids examined from cases of chickenpox which had apparently been initiated by a case of zoster showed scanty elementary bodies but these were the same typical brick-shaped bodies seen in the fluid from the original case of herpes zoster.

It is of interest to note that the site of the eruption in those cases of herpes zoster induced by trauma (lumbar puncture or *x* rays) conformed to the actual area of skin damaged and not to the area over the distribution of the segmental nerves from that region.

The intranuclear inclusion bodies seen in the epithelial cells lining the skin vesicles support the hypothesis, suggested by the very early appearance of elementary bodies in the vesicle fluid, that the virus multiplies in the skin at an early stage of the clinical disease. Suspensions of the elementary bodies from the vesicle fluid of one case of herpes zoster were agglutinated strongly by convalescent sera from cases of zoster and varicella and also to some extent by serum from cases of the acute phase of varicella or adult serum. *H. J. Bensted*

BACTERIA

2362. **Studies on the Coagulase-reacting Factor. II. Properties of Coagulase-reacting Factor, and Relation to Blood Clotting Components**
M. TAGER and H. B. HALES. *Journal of Immunology* [*J. Immunol.*] **60**, 1–9, Sept., 1948. 15 refs.

Twenty specimens of normal human plasma were titrated for coagulase-reacting factor (C.R.F.) against a preparation of staphylococcal coagulase and gave similar values. Of a variety of animal plasmas tested human and rabbit plasma were most reactive and those of chicken and guinea-pig only slightly so. The factor may either be absent from certain specimens of plasma of the two latter species or its action may be masked or inhibited; the latter possibility is suggested by the demonstration of the factor after precipitation by the Mellanby technique in certain samples, which otherwise gave negative results. C.R.F. was demonstrated in various tissues of the rabbit; this activity may be due to the plasma contained in the tissues, although the fact that higher values are obtained with the lungs than with the more vascular liver suggested that the tissues might have activity independent of the plasma.

Loss of C.R.F. was not noted in plasma stored for 115 days in the ice-box or 7 days at 37° C. C.R.F. was stable at *p*H 6 to 9; it was not inactivated by heating for 30 minutes at 54° C., but was partially destroyed by heating at 55° C. for 30 minutes.

The possible identity of C.R.F. with the components of the blood concerned is discussed. Its relative heat-stability and ability to pass a bacterial filter distinguished it from fibrinogen, from which it could be separated by ethanol precipitation. Calcium ions were unnecessary for the coagulase reaction. Materials, such as platelet suspension and an acetone-extracted preparation of rabbit brain which are rich in thrombokinase, were less active against coagulase than whole plasma. On the other hand, C.R.F. had many properties in common with prothrombin, although there were important differences. Repeated Seitz filtration of plasma led to loss of prothrombin with a retention of C.R.F. activity. Some prothrombin, however, could be demonstrated in the filtrate after precipitation and concentration. A preparation of thrombin, in which prothrombin might be presumed to have been converted, was highly active against coagulase. Inconclusive results were obtained when attempts were made to test purified preparations of prothrombin and the relation of C.R.F. to prothrombin remained uncertain. *D. G. ff. Edward*

2363. **Observations on the Biochemical and Serological Characteristics of *Pseudomonas pyocyanea***
R. CHRISTIE. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 425–437, Sept., 1948. 20 refs.

The genus *Pseudomonas* comprises those bacilli which produce pigments derived from phenazine, water-soluble fluorescent pigments, or both. Other characteristics of the genus include failure to ferment lactose, formation of ammonia, and utilization of citrate.

The only biochemical or cultural tests found reliable for species differentiation were haemolysis on (sheep) blood agar in 2 or 3 days at 25° C. (the haemolysin is not filtrable), and growth at 37° C. Strains of human origin grew well at 37° C. and at 25° C. and were haemolytic; non-human strains grew poorly at 37° C. and were non-haemolytic. The two species *Ps. aeruginosa* (*pyocyanea*) and *Ps. fluorescens* may thus be differentiated and each can be further subdivided into a number of serological groups possessing different somatic antigens; in the case of *Ps. aeruginosa* the groups may be further subdivided into types by the possession of 1 of 2 (or possibly more) flagellar antigens. Other criteria such as the fermentation of glucose, action on milk (clotting, peptonizing, liquefying), and the production of pyocyanin are of less value since the considerable subdivision possible on this basis is not correlated with serology or source of the strains and, as is also the case with pathogenicity, results tend to vary in degree.

It is suggested that the specific name *pyocyanea* for the human pathogen is preferable to *aeruginosa* and that the latter name should replace *fluorescens* for the saprophyte.

[The author correctly states that the ability to produce pyocyanin (which is blue, only assuming the green colour when partially changed to acid α-oxyphenazine) and fluorescein can vary from strain to strain. The inability to produce either is no evidence of species differentiation. He fails to make clear that the production of the former identifies its producer as *Ps. aeruginosa*. From a practical point of view unless one of these pigments is produced the presence of a pseudomonas species is unlikely to be suspected, and, in a yellowish medium, the green or greenish-blue colour of pyocyanin, when confirmed by extraction with chloroform, remains the most important criterion of the

presence of *Ps. aeruginosa* in a culture, though serology may well be of subsequent value in tracing the source of infection. The inclusion of sewage as a source of " non-human " strains seems a little odd.] *G. T. L. Archer*

2364. **The Bacteriological Interpretation of Vaginal Smears**

N. LAUGHTON. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 262–263, Sept., 1948. 3 figs., 8 refs.

Vaginal smears were examined, and cultures were made, from 39 women. Döderlein's bacillus (*Lactobacillus acidophilus*) was usually recognized without difficulty in the former, and was cultured from 21 individuals. The commonest organisms, however, were corynebacteria (isolated from 33 cultures). In direct films these were sometimes Gram-negative and of a curved shape (the latter being possibly due to fixation in a viscous medium) and hence might be mistaken for vibrios (the presence of which has sometimes been suspected) since the use of special media failed to produce any growth of vibrios. Cocci were usually not abundant in direct smears but 29 cultures were positive for staphylococci, and *Diplococcus crassus* (which could be mistaken for the gonococcus) was isolated from 10 persons. In two direct smears slender Gram-negative filaments, possibly of *Streptobacillus moniliformis*, were observed. No attempt was made at confirmatory culture.

G. T. L. Archer

2365. **The Effects of Nitrogen Mustard on *Escherichia coli***

V. BRYSON. *Journal of Bacteriology* [*J. Bact.*] **56**, 423–433, Oct., 1948. 4 figs., 12 refs.

The mutation of T2-phage-sensitive strains of *Bacterium coli* B to phage-resistant strains was induced by nitrogen mustard (HN-2) acting on cultures unaffected by the toxicity of the chemical agent. Cultures resisting the toxic action of HN-2 were chosen by progressive selection. It was found that this toxic resistance was related to the resistance of the same culture to ultraviolet irradiation, and it seems likely that these related properties may involve an identical mechanism. This phage-sensitiveness to phage-resistance mutation is more readily induced by ultraviolet irradiation than by nitrogen mustard, but the author considers that specific chemicals would offer a more precise mechanism for " altering the chemical structure of the bacterial cell to produce directed genetic modification ". *H. J. Bensted*

2366. ***Streptomyces venezuelae* n. sp., the Source of Chloromycetin**

J. EHRLICH, D. GOTTLIEB, P. R. BURKHOLDER, L. E. ANDERSON, and T. G. PRIDHAM. *Journal of Bacteriology* [*J. Bact.*] **56**, 467–477, Oct., 1948. 3 figs., 5 refs.

The recently discovered antibiotic chloromycetin was obtained from culture filtrates of a species of *Streptomyces* isolated from a soil sample in Venezuela, and the name *Streptomyces venezuelae* is now proposed. Since this organism bears some resemblance to the streptothricin-producing *Streptomyces lavendulae* the various properties of the two organisms have been compared. There are differences in morphology and biochemical reactions, but the most striking distinction lies in the yield of antibiotic substance. Under conditions most favourable to the production of the particular antibiotic *Streptomyces venezuelae* yielded practically only chloromycetin, and *Streptomyces lavendulae* streptothricin. This was confirmed by fractionation of the filtrates. Actinophage experiments and precipitin tests provided further evidence that strains of *Streptomyces venezuelae* belong to a species distinct from *Streptomyces lavendulae*. *H. J. Bensted*

2367. **Mutation in a Single-cell Culture of *Corynebacterium diphtheriae***

W. GOLDIE, M. GORDON, and K. I. JOHNSTONE. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 369–377, July, 1948. 8 figs., 17 refs.

Two of the rare *Corynebacterium diphtheriae* strains showing mutation from one colonial form into another have in this study been investigated for the first time by the single cell culture technique. Thus it has been established beyond doubt that the observed mutation of *C. diphtheriae* intermedius into gravis colonies is not an apparent one due to an originally mixed culture of both types but is a genuine mutation which must be due to changes occurring in the bacterial genes. The 2 strains investigated in this way were isolated from 2 unconnected cases of clinical diphtheria in immunized individuals and occurred in the same rural area. On first isolation all the characteristics of intermedius colonies were present though the strains fermented starch—one of the characteristics of the gravis type. On continued incubation of tellurite culture plates papillae were formed on the majority of the small intermedius colonies. After further 48 hours' incubation the papillae grew into typical large gravis colonies, thus completely obscuring the previous intermedius appearance. The microscopical differences between intermedius and gravis strains of *C. diphtheriae* were observed in the 2 phases of the strains. Both phases were distinguished by rather slow glucose fermentation [a feature which has been noticed recently by Frobisher in U.S.A. in a variety of intermedius strains labelled, perhaps rather unfortunately, type minimus by this author].

Mutation occurs on all media containing blood but not, or only to a very slight extent, on nutrient agar and serum agar plates. Although in the intermedius phase the colonies of these 2 strains in no way differ from the usual intermedius colonies on the usual media a 50% serum-0·0125% cystine-agar medium reveals the different nature of these strains. Although they remain in the intermedius phase they form on this medium colonies of the size of gravis strains while typical intermedius strains grow as rather small colonies.

Inhibition of mutation occurring in Hiss's serum water enabled the authors to establish beyond doubt that starch fermentation occurs in both the " intermedius " and " gravis " phases, a further proof of the special position of these apparent intermedius strains. Reversion of the " gravis " phase to the " intermedius " phase

was not observed spontaneously nor could it be induced. From guinea-pigs infected with the " intermedius " phase only this phase was isolated from necropsy material, but in one of the two clinical cases the " intermedius " phase was soon replaced by the gravis mutant, which was similarly characterized by exceptionally slow glucose fermentation. The significance of these strains is difficult to assess at the moment. [The 3 main *C. diphtheriae* types have been found constant by most observers. Changes of type distribution, however, may occur in any given population. The direction of such changes usually observed is from mitis to intermedius or mitis to intermedius to gravis, often heralding an outbreak of epidemic severity and proportions. The question arises whether mutations as described in this paper are spontaneous or whether the mutations have been induced by conditions outside the bacterial cell, as for instance by propagation in immunized individuals or an immunized community. It is remarkable that both patients from whom the strains were isolated had been immunized before infection. A point which seems worthy of further investigation is the relative quantitative toxin production of the two phases of such mutating strains.] *K. S. Zinnemann*

2368. **The Inhibitory Effect of Iron Salts on the Pathogenicity of *Corynebacterium diphtheriae* in the Guinea-pig.** (Tlumivý účinek solí železa na pathogenitu *Corynebacterium diphtheriae* na morčeti)
J. Málek. *Časopis Lékařů Českých* [*Cas. Lék. čes.*] **87**, 992–996, Oct. 1, 1948. 10 refs.

In five experimental series guinea-pigs were injected subcutaneously both with varying doses of *Corynebacterium diphtheriae* (gravis and mitis types) and with varying amounts of inorganic and organic iron compounds (potassium ferricyanide, iron ammonium citrate, and so on). A marked inhibitory effect on the pathogenicity of *C. diphtheriae* was seen after simultaneous subcutaneous injection of pathogenic organisms and the inorganic salts; organic iron salts and those salts in which iron formed a part of the anion complex were ineffective. The degree of inhibition *in vivo* varied with the number of organisms injected into experimental animals; the minimal quantity of iron required to inhibit the pathogenic effect of 500×10^6 organisms was 10 μg. per litre of fluid. There was no appreciable difference in the sensitivity to iron compounds of gravis and mitis types of *C. diphtheriae*. *H. P. Fox*

2369. **I. Pathogenic-apathogenic Transformation of *Salmonella typhi-murium*.** [In English]
O. Maaløe. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 414–430, 1948. 2 figs., 7 refs.

Variation in invasiveness between non-pathogenic and pathogenic strains of *Salmonella typhi-murium* is stated to be due mainly to difference in resistance to complement. No significant difference in toxicity was observed between the strains, and they were identical morphologically and antigenically. The occurrence of temporary reversible loss of resistance as opposed to the above-described permanent mutative loss of pathogenicity and resistance is reported. Temporary loss of resistance to complement was found when the resistant strain was grown in diluted broth; glucose and several other nitrogen-free compounds in the broth prevented the change. Phloridzin lowered resistance considerably, and glucose counteracted this effect to some extent. *Joyce Wright*

2370. **Slide Agglutination of *Bacterium coli* var. *neapolitanum* in Summer Diarrhoea**
J. Bray and T. E. D. Beavan. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 395–401, July, 1948. 11 refs.

This investigation represents the continuation of one made in 1943 when a particular serological type of *Bacterium coli* (namely var. *neapolitanum*), recognized by a late fermentation of maltose, was found in association with summer diarrhoea of infants (*J. Path. Bact.*, 1945, **57**, 239). During 1945 faecal cultures were made from 40 cases of gastro-enteritis in infants and from 80 patients without diarrhoea. Three-quarters of the cases were severe; there was a mortality rate of 28%, necropsy findings being insignificant. From each culture on MacConkey's agar one colony was tested on a slide for agglutination with a rabbit antiserum to *Bact. coli* var. *neapolitanum*. Positive slide agglutination was later confirmed by tube agglutination, and biochemical reactions were checked. Colonies of *Bact. coli* var. *neapolitanum* were identified in cultures from 87·5% cases of gastro-enteritis and from only 4% of the controls. Reciprocal tests, including agglutinin-adsorption tests, suggested that the strains isolated were antigenicaly similar to those isolated in 1943. The new strains, however, did not exhibit the late fermentation of maltose noted previously. It is suggested that there is a type of gastro-enteritis in bottle-fed infants with a high mortality, in which the coliform flora of the gut tends to be replaced by a single type. *D. G. ff. Edward*

2371. **Starch-fermenting Gelatin-liquefying Corynebacteria Isolated from the Human Nose and Throat**
W. H. H. Jebb. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 403–412, July, 1948. 22 refs.

Twenty-six strains of a gelatin-liquefying corynebacterium were investigated and their properties were compared in detail with those of other species of corynebacterium, particularly *C. diphtheriae gravis* and *C. ovis*, which they most resemble. They fermented glucose, maltose, and starch. A late fermentation of trehalose and a failure to reduce nitrates were properties, which, together with the liquefaction of gelatin, helped to distinguish them. One strain was injected subcutaneously into guinea-pigs; death of the animal was prevented by the administration of diphtheria antitoxin [with other strains death cannot always be prevented]. When injected intradermally into guinea-pigs all strains produced local oedematous lesions, which ulcerated and often formed pus. The lesions were not prevented by a dose of 1,000 units of diphtheria antitoxin which prevented lesions due to *C. diphtheriae*, but not those due to *C. ovis*.

It is believed that the toxin produced by the gelatin-liquefying strains, although similar to diphtheria toxin, contains a component resembling that of *C. ovis*. No conclusions are drawn as regards the epidemiological importance of the organism. *D. G. ff. Edward*

2372. **The Kappa and Lambda Antigens of *Clostridium welchii***
C. L. OAKLEY, G. H. WARRACK, and M. E. WARREN. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 495–503, July, 1948. 1 fig., 9 refs.

When injected intramuscularly into guinea-pigs and mice the κ toxin in *Clostridium welchii* filtrates produced a local swelling. The antitoxin in sera could be measured by its ability to inhibit this effect. The intracutaneous injection of guinea-pigs with toxic filtrates caused necrotic lesions, and intravenous injection into mice resulted in lung haemorrhages and death. Neither of these effects afforded a satisfactory method for estimating antitoxin. These effects in animals appeared to be caused by the κ toxin and were due to destruction of the collagen in the tissue. κ toxin appeared to attack gelatin. Antitoxin could be estimated by treating columns of gelatin-agar with toxin-antitoxin mixtures and afterwards measuring the effect on the gelatin by treating the columns with mercuric chloride. [The original paper should be consulted for details of the test.]

A toxin attacking azocoll and hide powder, and which was not κ toxin, was found in *Cl. welchii* type B filtrates. This toxin, called λ, did not attack collagen or soften muscle. The use of azocoll or hide powder is therefore not satisfactory as a test for collagenase. Gelatin appeared to be attacked by λ. Fresh normal horse sera contained a substance neutralizing λ; the immunization of horses stimulated the production of a specific neutralizing antitoxin for λ. Under suitable conditions *Cl. welchii* types A and C produce κ toxin; type B produces λ and type E (Bosworth) both κ and λ. Strains of type D vary, producing either κ or λ, or both of them together, or neither. *D. G. ff. Edward*

2373. **The Action of Lysozyme on Heat-killed Gram-positive Micro-organisms**
M. WEBB. *Journal of General Microbiology* [*J. gen. Microbiol.*] **2**, 260–274, Sept., 1948. 12 figs., 32 refs.

After centrifugation of cultures of *Clostridium welchii*, *Streptococcus faecalis*, and *Staphylococcus aureus*, the organisms were re-suspended in distilled water and killed by rapidly heating to 80° C. and maintaining at this temperature for 30 minutes. The suspension was incubated with lysozyme solution containing 1 mg. of the enzyme per ml. and buffered with phosphate, smears being made at intervals to determine the proportion of organisms converted to the Gram-negative form. All the Gram-positive organisms studied, with the exception of yeast, became completely Gram-negative when incubated with lysozyme. The conversion was optimal at *p*H 6·0, and the factor responsible was not ribose nuclease. Small amounts of reducing sugar were liberated during the action of lysozyme on the killed cells, and it was shown that the reaction involved partial hydrolysis of cell surface material with removal of small amounts of specific carbohydrate and of ribose nucleic acid fractions from the cell surface, the constitution of which was determined. Extraction of the cells rendered Gram-negative by lysozyme yielded a fraction giving positive Molisch and negative biuret reactions, and a fraction giving positive biuret, ninhydrin, and Sakaguchi reactions and negative Millon, sulphur, and Molisch reactions. The latter fraction appeared to be an acid protein or polypeptide. *P. B. Marshall*

2374. **Investigations on the Dissociation of the Rough Form of Sonne Dysentery Bacilli into the Smooth Form.** (Untersuchungen über die Umwandlung der Flachform in die Rundform des E-Ruhr-Keimes)
C. LUCASSE. *Schweizerische Zeitschrift für Pathologie und Bakteriologie* [*Schweiz. Z Path. Bakt.*] **11**, 306–328, 1948. 19 refs.

Three different colony types of the Sonne dysentery bacillus are known—the round smooth form, the rough flat form, and a mixture of the two. The latter colony type has been likened to a bursting bombshell. The rough variant dissociates readily from smooth type cultures but dissociation of typical smooth colonies from rough strains has never been observed with any certainty. In view of the facts that after some time convalescent patients excrete only rough strains, that man is the main reservoir, and that the smooth variant is far more virulent and is probably solely responsible for acute infections, the question arises where in nature dissociation of the smooth from the rough form takes place.

The author kept 7 rough strains for long periods and under different conditions on the surface of apples and of carrots, in sterile and non-sterile milk, in water, and in sterile soil. Although smooth colonies were obtained from all these substrates these colonies never agglutinated with an S serum absorbed with an R strain. Cultures from these S colonies were never pathogenic to animals. Addition of various chemical compounds to cultures on solid and in fluid media—with the intention of creating more favourable conditions for complete dissociation of these smooth colonies into the agglutinable and virulent S form—was without results. Equally unsuccessful were repeated parenteral passages through rats and guinea-pigs. The apparent S colonies must, therefore, be regarded as pseudo-smooth variants. The only tangible result from these extensive experiments is the observation that R strains were able to survive at room temperature in the dark on the surface of apples for 15 days, on carrots for 38 days, in sterile milk for 129 days, in water for 111 days, and in soil for 95 days. *K. S. Zinnemann*

2375. **The Mechanical Destruction of Bacteria**
H. K. KING and H. ALEXANDER. *Journal of General Microbiology* [*J. gen. Microbiol.*] **2**, 315–324, Sept., 1948. 4 figs., 2 refs.

The authors have investigated the destruction of bacteria by shaking with small glass particles; 40 ml. of a bacterial suspension was placed in a 4-ounce (113·6 ml.) bottle

with 50 g. of glass beads of an average diameter of 0·26 mm., and the whole was shaken in an ordinary shaking machine at 300 strokes, with an amplitude of 2½ in. (6·25 cm.) per minute., At intervals samples of fluid were withdrawn and viable counts were made. The percentage of viable organisms declined logarithmically to a certain level, and then remained more or less constant, indicating that a proportion of the organisms were resistant to mechanical destruction. The destruction of *Bacterium coli* proceeded logarithmically for 10 hours, after which the numbers remained constant. The count could not be reduced by transferring the contents to another bottle and shaking for a further period, while a small quantity of a concentrated bacterial suspension introduced into the same bottle was destroyed in the usual manner, showing that the presence of cell debris was not obstructing the grinding process. The constancy of the final count could not be attributed to multiplication of the residual organism. Resistance to mechanical destruction was not inheritable, as cultures from residual organisms were destroyed at the normal rate. The relative susceptibility of various organisms was investigated, together with the proportion of resistant cells; *Staphylococcus aureus* was most, and *Mycobacterium smegmatis* least, susceptible to mechanical destruction; the proportion of resistant cells varied from 1 in 1,000,000 for the former organisms to 1 in 100 for *Bacillus mesentericus*. Yeast was more resistant than any of the bacteria studied. No correlation was found between resistance to shaking and resistance to heat or to penicillin, or the age of the culture; there was some correlation between capsulation and susceptibility to mechanical damage in *Aerobacter* and *Pneumococcus*.

D. J. Bauer

2376. **Bacterial Flagella as Active Organs of Motility.**
(Über Bakteriengeisseln als aktive Bewegungsorgane)
F. KAUFFMANN. *Schweizerische Zeitschrift für Pathologie und Bakteriologie* [*Schweiz. Z. Path. Bakt.*] **11**, 378–381, 1948. 5 refs.

Pijper (*J. Path. Bact.*, 1946, **58**, 325) put forward a hypothesis that bacterial flagella are not active organs of motility but filaments formed from a soft envelope around bacterial cells. According to his view these filaments are formed when bacteria move against the resistance of a fluid medium, and motility is a function of active movements of the bacillary body.

Against this view the author advances a number of arguments. (1) Flagella are present in variants of *Salmonella* which possess H antigen and are agglutinable by H sera but have lost motility completely. In these strains flagella cannot have been formed in consequence of motility. (2) Non-motile variants of *Salmonella* possess only O antigen. If flagella are only filaments formed from an outer envelope of bacteria there is no reason why non-motile variants should not have this outer envelope and thus be agglutinable with H antigen. (3) Flagellated bacteria become non-motile after addition of H antigen to a suspension of bacteria. If motility were a function of the bacillary body the bacteria would remain motile after the action of anti-serum on the flagella. (4) Motility is not inhibited after addition of O serum to a motile culture suspension. The author does not dispute the fact that active movements of the bacillary body occur, but holds that these are not responsible for bacterial motility. *K. S. Zinnemann*

2377. **The Action of Urea and Some of its Derivatives on Bacteria. VIII. The Antibacterial Activity of Hexyl Carbamate, Alone and in Combination with Sulfonamides, and its Effect on *para*-Aminobenzoic Acid**
L. WEINSTEIN. *Journal of Immunology* [*J. Immunol.*] **59**, 331–333, Aug., 1948. 9 refs.

Hexyl carbamate showed bacteriostatic, but not bactericidal, activity. *Bacterium coli*, *Salmonella typhi*, and *Shigella paradysenteriae* were inhibited by 0·08% hexyl carbamate, *Pseudomonas aeruginosa* and *Proteus vulgaris* by 0·1%, and *Salm. schottmülleri* by 0·06%. Addition of a non-bacteriostatic concentration (0·05%) of hexyl carbamate to non-inhibiting concentrations of sulphanilamide markedly suppressed the multiplication of *Bact. coli*, *Ps. aeruginosa*, and *P. vulgaris*. As with other carbamates, hexyl carbamate inhibited the antisulphonamide activity of *p*-aminobenzoic acid, but only slightly with non-bacteriostatic concentrations (0·03 to 0·05%). Comparison with previous work shows that the bacteriostatic activity of hexyl carbamate is 5 times that of butyl and *iso*butyl urea, 30 to 50 times that of urethane, and 60 to 100 times that of urea, indicating that in this series activity increases with the number of carbon atoms in the alkyl substitutive chain. *P. B. Marshall*

2378. **Effect of Different Methods of Coagulation of Culture Media on Tubercle Bacilli Growth**
M. M. CUMMINGS, M. C. DRUMMOND, and G. T. LEWIS. *Public Health Reports, Washington* [*Publ. Hlth Rep., Wash.*] **63**, 1305–1312, Oct. 1, 1948. 10 refs.

Recent investigations have emphasized the importance of the inhibition of growth of the tubercle bacillus by traces of free fatty acid in the culture medium. The authors considered that the deleterious effect of overheating egg media might be explained along these lines; they therefore carried out experiments to determine the possible presence and relative concentration of free fatty acids, or similar substances, in lots of culture media prepared by inspissation and autoclaving. Those used were Loewenstein–Jensen medium and a modification of the Petragnani medium. Coagulation of both media was accomplished by inspissating at 80° to 85° C., and by autoclaving at a temperature of approximately 100° C., keeping all valves closed, except the steam inlet, thus retaining the original air inside the autoclave. The time of coagulation was measured from the moment the desired temperature was reached, and was varied within feasible limits—90 and 40 minutes for inspissation, and 90, 40, 30, and 20 minutes for autoclaving. Ether-soluble acidic material was extracted from the media, before and after heating, by a method described fully in the paper. It was found that this material, some of which was presented before the media were heated, was increased by heating. For example, titration values,

expressed as mg. of alkali required for neutralization of 1 g. of dried sample, in the case of autoclaved media were more than double those for inspissated material. Time, however, as well as temperature, is a factor in the process, as, in the case of the 90-minute inspissated material, values were only slightly lower than the range of values obtained for autoclaved media. On the other hand, variation in the time during which the medium was autoclaved, between 20 and 90 minutes, had no effect on the titration values.

When the H37 Rv strain of tubercle bacillus was grown on the media heated at 85° C. and 100° C. for 40 minutes it was found that the results correlated well with the chemical findings. The amount of growth obtained, as measured by the number of calories, decreased as the amount of ether-soluble acidic material in the medium increased. *T. D. M. Martin*

IMMUNITY

2379. **Precipitin Reactions in Experimental Histoplasmosis and Blastomycosis**
A. L. PATES. *Science* [*Science*] **108**, 383–385, Oct. 8, 1948. 3 refs.

Skin tests and complement-fixation tests have been used for histoplasmosis and blastomycosis. Broth-culture filtrates of the saprophytic mycelial phase and suspensions of the yeast-like parasitic forms have been employed. The former gave non-specific reactions, the latter appear to be more specific in complement fixation than in skin tests. Previous studies of precipitin tests have been limited and inconclusive.

The author has performed precipitin reactions, using a ring test in which 0·1 ml. of falling dilutions of antigen was layered on 0·1 ml. of serum of rabbits infected experimentally by intravenous inoculation of the yeast-like phase of *Histoplasma capsulatum* and *Blastomyces dermatitidis*; presence or absence of a precipitate was noted after 2 hours at 37° C. Antigens used consisted of filtrates of broth cultures of the mycelial phase of the two species, and fractions of that of *H. capsulatum*. These fractions were prepared by adjustment of the *p*H to 4·2 and 11·2 respectively after addition of 1 volume of 95% ethyl alcohol. The precipitates after centrifuging were dissolved in distilled water. Two fractions were obtained from each of these solutions by: (*a*) simple adjustment of the *p*H to the alkaline or acid reactions respectively (fractions 1 and 3—the former being protein-like, the latter undetermined), and (*b*) addition of 1 volume of alcohol to the acid material (fraction 2—polysaccharide) and 2 volumes to the alkaline material (fraction 4—polysaccharide). It was shown that crude filtrates and fraction 1 were non-specific, giving positive reactions in animals infected with both organisms, fractions 2, 3, and 4 being more specific for *H. capsulatum*. The last, however, while the most specific, did not react with all animals inoculated with the homologous organism. Tests at 2, 3, 5, 7, and 9 weeks showed that antibodies to fractions 2, 3, and 4 disappeared more rapidly than those to the other antigens employed.

In skin tests with these antigens fractions 1 and 2 were not specific, fraction 3 gave negative results, and fraction 4 produced a specific response. Normal animals failed to react. *G. T. L. Archer*

2380. **The "Inhibition" of Isoagglutinin Activity by Human Plasma and its Fractions**
F. HOMBURGER and M. MELIN. *Journal of Immunology* [*J. Immunol.*] **60**, 47–55, Sept., 1948. 1 fig., 16 refs.

Inhibition of isoagglutination in plasma pools is, in the opinion of the authors, due to group-specific agglutinogens, and not to non-specific factors. The agglutinogens are widely distributed among the plasma fractions. *C. L. Oakley*

2381. **A Skin-test Antigen Common to Five Viruses of the Psittacosis–Lymphogranuloma Group**
L. KILHAM. *Journal of Immunology* [*J. Immunol.*] **60**, 157–165, Sept., 1948. 12 refs.

Rabbits infected with mouse tissues containing psittacosis, meningopneumonitis, lymphogranuloma venereum, mouse pneumonitis, or feline pneumonitis virus give positive skin-test reactions with preparations made from yolk sac infected with any of the five viruses. Control uninfected animals were not sensitive. Sera from all the infected animals gave complement fixation with "lygranum C.F.," a proprietary preparation made from lymphogranuloma virus. *C. L. Oakley*

2382. ***Hemophilus pertussis* Soluble Antigen and Complement Fixing Antibodies**
I. A. PARFENTJEV and M. E. VIRION. *Journal of Immunology* [*J. Immunol.*] **60**, 167–171, Sept., 1948. 12 refs.

Sterile filtrates of formalized cultures of *Haemophilus pertussis* fix complement in the presence of *H. pertussis* antibacterial sera prepared in horses or rabbits, and of the sera of children with whooping-cough. Mild peptic digestion of complement-fixing *H. pertussis* rabbit or horse antisera destroyed the complement-fixing antibody without affecting the antitoxic antibodies. Peptic digestion of *H. pertussis* filtrates does not destroy the complement-fixing antigen. *C. L. Oakley*

2383. **The Effect of Roentgen Irradiation on Antibody Formation in Rabbits**
C. G. CRADDOCK and J. S. LAWRENCE. *Journal of Immunology* [*J. Immunol.*] **60**, 241–254, Oct., 1948. 4 figs., 33 refs.

Roentgen irradiation of rabbits with a dose (250 r, whole body) sufficient to cause degenerative changes in lymphoid tissue and marked lymphopenia without general deleterious effect is associated with marked reduction of the animal's power to produce antibodies to typhoid vaccine or to sheep red cells. Lymphopenia continues for 30 days or so after irradiation; thereafter the lymphocyte count rises rapidly to normal; animals that have recovered in this way show normal antibody responses. If irradiation is delayed until antibody response has reached its peak, or to a time just before

that peak is expected, it does not impair antibody production, though degeneration of lymphoid tissue and lymphopenia still occur. No anamnestic reaction could be elicited by irradiation with small doses of *x* rays of rabbits whose antibody levels had reached a steady state.

The authors conclude that the depressant effect of *x*-irradiation on antibody production cannot be entirely due to depression of lymphoid tissue. *C. L. Oakley*

2384. **An Unusual Type of O Agglutination**
C. A. STUART, ROBERT FEINBERG, and RICHARD FEINBERG. *Journal of Bacteriology* [*J. Bact.*] **56**, 419–422, Oct., 1948. 7 refs.

A strain of *Shigella alkalescens*, though normally giving typical heavy compact granular O agglutination with its homologous antiserum, gave occasionally, under the same conditions, a fine thready imperfect agglutination readily dispersible on vigorous shaking. Similar observations were made with some strains of *Paracolobactrum*, *Proteus rettgeri*, and *Salmonella ballerup*. Thready agglutination may in some instances be correlated with the Vi antigen. The substances responsible are relatively thermostable, easily dissociated from the cell, and seem to be associated with a phospholipid constituent of the cell. Saline and alcohol extracts of many enterobacteriaceae restore O-agglutinability to cultures showing thready agglutination.

The authors regard thready agglutination as an example of O-inagglutinability, and note that the amount of heating required to restore O-agglutinability to the cultures varies greatly in different cultures.
C. L. Oakley

2385. **Studies on Immunity and Serology of Influenza.** (Untersuchungen zur Immunität und Serologie der Influenza)
H. RAETTIG. *Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten* (*Abteilung* I, *Originale*) [*Zbl. Bakt.* (I. *Abt. Orig.*)] **152**, 381–402, 1948. 8 figs., bibliography.

In this paper (the third of a series) the author deals with the specificity of the Hirst agglutination-inhibition test, and with the specificity of the immune bodies demonstrated by this method. The investigations, involving more than 6,000 serological tests by Hirst's method as well as 402 animal experiments and tests with 200 human sera from the subjects actively immunized against influenza, were planned to demonstrate: (*a*) a correlation between the agglutination-inhibition titre and virulence; (*b*) formation of immune bodies in animals; (*c*) an increase in the titre of immune bodies in men after prophylactic inoculation; (*d*) agglutination reactions with the porcine strain of the influenza virus, and (*e*) a non-specific increase of the agglutination-inhibition titre in persons suffering from lung disease and tuberculosis. Results are discussed in relation to the evidence in the available literature. Data are also given on the normal level of specific antibodies in relation to age, sex, pregnancy, and season. In general, it was established that the degree of immunity found in human beings or animals after an attack of the disease or active immunization against it is commensurate with the titre of serum antibodies as revealed by serological tests. Vaccination with identical or related (porcine strain) antigens resulted in a perceptible increase in titre of immune bodies. This explains an increase in the agglutination-inhibition titre seen in subjects with lung disease or tuberculosis, for in those persons influenza organisms appear as a result of secondary infection.
H. P. Fox

2386. **Prophylactic Immunization Against *Streptococcus sanguis***
E. ALTURE-WERBER and L. LOEWE. *Journal of Bacteriology* [*J. Bact.*] **56**, 391–395, Oct., 1948. 10 refs.

The authors immunized 56 patients who had recovered from subacute bacterial endocarditis with a polyvalent vaccine of *Streptococcus sanguis* (probably the same as *Streptococcus* s.b.e.) in the hope of preventing relapse infections with this organism. After a course of intradermal and subcutaneous injection of the vaccine [the method of preparation is not specified] most of the patients developed agglutinins to the organism, persisting for 27 weeks after the first injection. Reactions were slight. *C. L. Oakley*

2387. **The Mechanism of the Effect of *X*-rays on Bacterial Toxins**
E. EPHRATI. *Biochemical Journal* [*Biochem. J.*] **42**, 383–389, 1948. 25 refs.

Tetanus toxin and staphylococcus haemolysin were destroyed by exposure to *x* rays; purification of tetanus toxin greatly increased its susceptibility to destruction by this means. In both cases antigenicity was lost as well as toxicity, and the method cannot, therefore, be used to prepare toxoids. Certain proteins, their partial and total hydrolysis products, reducing amino-acids, glutathione, thioglycollic acid, and ascorbic acid greatly increased the degree of exposure necessary to destroy the toxins; oxidizing substances had no such action. Presumably *x* rays cause the formation of oxidizing radicals in the water; these secondarily destroy the toxin by oxidation. Reducing agents "protect" the toxin by interfering with the secondary reaction.
C. L. Oakley

2388. **An Electrophoretic Study of Diphtheria Toxoid Preparations**
P. A. CHARLWOOD. *Biochemical Journal* [*Biochem. J.*] **42**, 425–428, 1948. 5 figs., 10 refs.

Electrophoretic examination of concentrated diphtheria toxoid in phosphate buffer (*p*H 8, $\mu=0{\cdot}1$) shows two major peaks, with sometimes a slow-moving minor peak. The major peaks are probably not homogeneous. One purified preparation appeared to be about 80% pure. Toxoid activity seems to be confined to the slower-moving major component. There appears to be no relationship between electrophoretic pattern of a toxoid and its antigenicity. *C. L. Oakley*

Paediatrics

2389. **Mechanism of Production of Acidosis in Premature Infants by Protein Milk**
W. S. HOFFMAN, A. H. PARMELEE, and A. GROSSMAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **75**, 637–659, May, 1948. 11 refs.

The powdered protein milk used in these experiments was made by precipitating casein from cow's milk by adding calcium chloride, and then adding the casein to whole milk. Apparently the resulting product contained considerable quantities of calcium chloride. This milk, when fed to 3 premature infants, produced a chloride acidosis within 3 days. Balance studies on a further 5 premature infants analysed in detail the response of the electrolyte system of the infants to this induced acidosis. It was found that ammonia production was increased, but not enough to prevent the loss of sodium, which was excreted with the excess chloride. Some of the sodium came from intracellular sources, and was there replaced by potassium. Similar experiments on 10 full-term infants gave comparable results, but deviations from the normal electrolyte pattern were less pronounced owing to the greater renal maturity of these infants. Results are interpreted as confirming McCance's findings that the young infant's kidneys are relatively incapable of concentrating urine. *Douglas Gairdner*

2390. **A Newly Recognised Reflex for the Diagnosis of Intracranial Injuries Ensuing during Labour.** [In English]
I. ZÁDOR. *Paediatria Danubiana* [*Paediat. danub.*] **4**, 256–261, Nov., 1948. 6 refs.

The finger-flexion reflex which is usually present (Trömner's sign) in adults with pyramidal lesions was also found in 50 normal infants 1 to 6 days old. In a severely asphyxiated newborn infant this reflex was elicited in the left hand, but in the right hand an extension instead of flexion was provoked and the fingers " spread like the blades of a fan ". The infant died the following day, and at necropsy a subarachnoid haemorrhage was found in the lower third of the left precentral gyrus. The author suggests that, if the causal connexion between the intracranial lesion and the observed reflex is confirmed by further observations, this reflex may be of diagnostic value in the immediate post-natal period.
S. A. Doxiadis

2391. **Experimental Use of Testosterone Compounds in Premature Infants**
E. K. SHELTON and J. S. MARK. *California Medicine* [*Calif. Med.*] **69**, 339–340, Nov., 1948. 5 refs.

Testosterone, either as methyl testosterone 5 mg. daily orally or as testosterone propionate 4 mg. daily intramuscularly, was given to 74 infants weighing less than 2,000 g. at birth. Treatment was begun 12 hours after birth and continued for 3 weeks. A control group receiving no testosterone was also observed. The length of time taken to regain the birth weight and to attain a weight of 2,500 g. was noted in each infant. The babies were divided into two groups—those weighing between 1,000 and 1,500 g. and those between 1,500 and 2,000 g. at birth. In the 1,000 to 1,500 g. group the untreated infants took an average of 14·7 days to regain their birth weight; those on methyl testosterone took 9 days, and those on testosterone propionate 7·5 days, to regain birth weight. Similar results were also recorded for the 1,500 to 2,000 g. group. It was found that the control group took an average of 42 days to attain a weight of 2,500 g. while the infants given methyl testosterone took 32 days and those receiving testosterone propionate 35 days.

Four pairs of twins were also observed; the larger twin in each pair was used as a control and the smaller was given testosterone. The smaller treated infants regained their birth weights more rapidly than did their larger untreated siblings.

Observation of the treated infants was continued during the first year of life. They all developed normally, no evidence of virilism being seen. No differences were visible in the development of long bones in the two groups at the end of one year. *L. M. Rose*

2392. **Dysostosis of Skull, Face and Extremities (Acrocephalosyndactyly)**
R. W. BUCKLEY and P. I. YAKOVLEV. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **75**, 688–694, May, 1948. 4 figs., 13 refs.

A syndrome of acrocephaly, facial deformities, syndactylism, and mental deficiency has been recorded under various titles—acrocephalosyndactylism, Crouzon's disease, and Apert's disease. In the present article the literature is reviewed, and a case of this syndrome is reported in a 12-year-old Italian boy.
Douglas Gairdner

2393. **Some Preliminary Analytical Data on Epidemic Illness of the Newborn in Obstetric Institutes.** (Некоторые предварительные данные анализов вспышек заболевания новорожденных в родовспомогательных учреждениях)
A. F. TURR. Педиатрия [*Pediatriya*] No. 6, 5–12, Nov.–Dec., 1948. 18 refs.

During the last few years epidemics of enteritis were observed among the newborn in obstetric institutions, and nothing short of closing down whole hospitals prevented these epidemics from spreading. The mortality rate was very high.

After vague prodromal symptoms, a severe septic syndrome develops. In severe cases pneumonia, otitis, and even encephalopathy are added to the enteric symp-

toms. Symptoms appear on the fourth to fifth day and the first cases are usually noted among premature babies. At necropsy, degenerative changes are seen in all parenchymatous organs, with severe catarrh of the mucous membrane of the alimentary tract. In less severe cases, the babies merely suffer from enteritis or gastro-enteritis. The pathological and clinical pictures are the same irrespective of the causative agent. Soviet workers are inclined to believe that the non-pathogenic group of bacteria present in the intestine become pathogenic if the barrier to infection becomes disturbed and a local process at first arises, which in some cases proceeds to bacteriaemia with toxaemia and then to septicaemia. The intestinal barrier may be disturbed by incorrect feeding, birth trauma, intercurrent illness, or admission to the intestine of massive doses of even innocent saprophytes. The younger the child the easier is this barrier disturbed. In the newborn and especially in premature infants, even under normal conditions, the intestine is probably permeable to certain bacteria and proteins. Hence there is no specific causative agent for epidemic enteritis, but various saprophytes and facultative pathogenic bacteria may be involved.

Breast-fed children resist the infection much better than babies who are either fed artificially or receive supplementary feeds of sterilized or pasteurized milk, even human milk. If supplementary feeds are necessary, they should consist of raw human milk, aseptically drawn off. Early diagnosis of enteritis is essential, followed by immediate isolation. *T. Guercken*

2394. **Hypovitaminosis A and B_1 in Clinical Features of Septic Conditions of the Newborn, I.** (A и B_1 гиповитаминозы в клинике септических заболеваний новорожденных)
B. B. KRETCHMER and S. A. BAYANDINA. Педиатрия [*Pediatriya*] No. 6, 12–18, Nov.–Dec., 1948.

During the war the number of newborn babies suffering from septicaemia and allied conditions increased enormously in children whose mothers had various illnesses during pregnancy. This work deals with immunity in relation to the vitamin intake of mother and child. The following factors were taken into consideration: (1) the state of immunity in septicaemia of the newborn and infants in the first few months of life; (2) hypovitaminosis A and B_1; (3) the content of vitamin A and B_1 in mothers who were breast-feeding their babies during illness. Clinically, the disease took on four forms: (1) umbilical sepsis; (2) pyaemia with formation of numerous abscesses; (3) toxic gastro-enteritis; (4) "septic conditions" (babies failed to gain weight, refused food, and so forth).

Hypovitaminosis A in newborn infants affects first of all the skin and mucous membranes, and there is a progressive dystrophy. Blood examinations were made during the illness, on improvement, and in convalescence. The children were divided into two groups. In group I, the vitamin was absent from the blood during the first two stages of the disease, but the carotene content was very high. This shows that the synthesis of vitamin A is delayed and a long period of regular intake is required before the vitamin content is restored. In group II, a great amount of the vitamin is present in the first stage of the disease, but it is rapidly used up and is absent in the other two stages. This hypervitaminosis may be due to disturbance in function of the reticulo-endothelial system, especially of the liver. The disturbance of synthesis of vitamin A lasts until full convalescence is reached, and synthesis is re-established more rapidly in mothers than in babies. In septicaemia liver function is disturbed and there is an excess of carotene in the liver. This may also account for the yellowish tinge of the skin. Most mothers had a low concentration of vitamin A in the blood with a high percentage of carotene.

The clinical picture of hypovitaminosis B_1 is little known. The mother's milk contains only traces of aneurin and newborn babies have none in the blood. Lack of vitamin B_1 leads to disturbances of respiration, digestion, and the nervous system and to a tendency towards oedema. Absence of vitamin B_1 in newborn babies causes anorexia, loss of weight, rigidity, and severe disturbances in the digestive system. In spite of large intake doses it appears in the blood only in the convalescent state. In fatal cases, death was mostly due to pneumonia. This hypovitaminosis leads to lowering of immunity and resistance, and under these conditions some non-pathogenic organisms become pathogenic.
T. Guercken

2395. **Toxoplasmosis in Children**
F. H. ADAMS, J. M. ADAMS, P. KABLER, and M. COONEY. *Pediatrics* [*Pediatrics*] **2**, 411–519, Nov., 1948. 14 refs.

The authors, working in the University of Minnesota Medical School, report 5 confirmed cases of toxoplasmosis and 8 strongly suspected cases. The main purpose of the paper is to point out that a patient in whom toxoplasmosis may be found at necropsy may show only a few of its cardinal manifestations clinically.

Toxoplasmosis in man may be congenital or acquired. The former type is usually fatal; the latter may be chronic, the patient surviving for years. Congenital visceral involvement may manifest itself by cyanosis and dyspnoea, hepatomegaly, and splenomegaly. The acquired form usually appears as an acute encephalitis or an atypical pneumonia with a maculo-papular rash. Manifestations of the disease are classified as follows: I. *Congenital toxoplasmosis.* A. Acute and chronic cases with neurological signs and symptoms—encephalomyelitis, hydrocephalus, convulsions, chorioretinitis, cerebral calcifications, microcephaly, anencephaly, and microphthalmus. B. Acute cases with visceral signs and symptoms—pneumonitis, myocarditis, hepatomegaly, splenomegaly, and jaundice. C. Latent cases. II. *Acquired toxoplasmosis.* A. Acute cases with neurological symptoms —encephalitis. B. Acute cases with visceral signs and symptoms—pneumonitis, exanthemata, and enteritis. C. Latent cases.

Of the 5 infants with proven toxoplasmosis, 2 were stillborn, and one 2 weeks, one 3 weeks, and one 4 months old. In the suspected cases patients varied in age from 3 weeks to 14 years. Toxoplasma-neutralization tests in the rabbit were carried out with the patients' sera, as

well as complement-fixation tests and antigen skin reactions. The majority of the results were positive, though the authors state in their introduction that the specificity of the neutralization test must be questioned.

When the paper was written 9 of their patients were alive. Convulsions were not noted as frequently as by other workers. The 5 patients with congenital disease all had hydrocephalus, though one patient was microcephalic despite the internal hydrocephalus. Cerebral calcification was found in 7 of the 14 cases. The spinal fluid showed pleocytosis and/or xanthochromia in 4 of the congenital and the 3 acquired encephalitic cases. The blood showed only slight eosinophilia. There was difficulty in isolating the toxoplasmic organism. In an addendum the authors mention a method of " re-activating " serum (for serological tests) which has been rendered inactive by being kept at room temperature for several days. *A. T. Macqueen*

2396. **The Significance of Positive Blood Cultures in Newborn Infants**
W. W. WADDELL, R. E. BALSLEY, and W. GROSSMANN. *Journal of Pediatrics* [*J. Pediat.*] **33**, 426–443, Oct., 1948. 8 figs., 2 refs.

Cultures were made of blood taken from 34 newborn babies in whom there were unexplained anorexia, listlessness, and undue weight loss. A haemolytic *Staphylococcus albus* was recovered in 21 cases, non-haemolytic *Staph. albus* in 3 cases, haemolytic *Staph. aureus* in 4 cases, and non-haemolytic *Staph. aureus* in one instance. In each case the skin was cleansed with iodine and alcohol, and the blood was obtained from the internal jugular or femoral vein. Repeat blood cultures in 23 of the 25 cases in which haemolytic staphylococci were found were again positive. As a control series cultures were made of blood taken from 50 newborn infants who did not show any sign of illness. A haemolytic *Staph. albus* was found in 13, non-haemolytic *Staph. albus* in 3, haemolytic *Staph. aureus* in 4, diphtheroids in 1, and hay bacilli in another. With one exception, all staphylococci recovered were coagulase-negative.

The authors discuss the possibility that the organisms were introduced by contamination, but consider that this was unlikely. They claim that the symptoms of anorexia, weight loss, and lassitude promptly disappeared when chemotherapy was started. They state that the skin of newborn infants is particularly rich in members of the staphylococcus group and that these organisms frequently invade the blood stream, often without producing symptoms.

[It would be extremely difficult to prove that coagulase-negative staphylococci recovered from the blood culture of normal healthy newborn infants were anything but the result of contamination.] *R. S. Illingworth*

2397. **Granulocytopenia in Children.** [In English]
L. SALOMONSEN. *Acta Paediatrica* [*Acta paediatr. Stockh.*] **35**, 189–201, 1948. 24 refs.

This paper deals only with " pure " granulocytopenia, those forms associated with such conditions as leukaemia or aplastic anaemia being excluded. The causes are classified as follows. (1) Infections, benign, as in granulocytopenia associated with certain exanthems. (2) Infections, malignant, the equivalent of agranulocytosis in British terminology. (3) Drugs, only sulphonamides being mentioned as a cause. The following types are also listed. (4) Post-infective, due to a brief transitory arrest of maturation of granulocytes. (5) Primary splenic granulocytopenia. There are two such cases reported in the literature, but as both were associated with anaemia and thrombocytopenia there seems no justification for including this group in the classification. (6) Cyclic granulocytopenia. Three cases have been reported, the fall in granulocyte count occurring at regular intervals of 3 weeks and being associated with fever, malaise, and ulcerative stomatitis. The aetiology is unknown. (7) Chronic granulocytopenia, a benign condition with vague symptoms, though there may be sudden acute attacks comparable to agranulocytic angina and quite unresponsive to treatment. The author reports one such case, and considers the condition a separate disease entity in children. *N. M. Jacoby*

2398. **Replacement Transfusion as a Treatment for Erythroblastosis Fetalis**
L. K. DIAMOND. *Pediatrics* [*Pediatrics*] **2**, 520–524, Nov., 1948.

In severe erythroblastosis foetalis anaemia progresses despite small repeated transfusions because the child's blood contains anti-Rh agglutinins in its serum; its red cells are coated with the same agglutinin so that they continue to be rapidly destroyed. This led to the idea of exchange transfusion.

Early attempts at using the cord for transfusion were not successful; the development of a synthetic polyethylene catheter overcame one of the difficulties. This material can be left in contact with human tissue for a long time without harm. The catheters are kept in a 1 in 1,000 solution of " zephrin alba " till needed, when they are washed through with warm sterile saline. The catheter is threaded into the umbilical vein and attached to a needle, this in turn to two three-way valves and a syringe. The umbilicus is washed clean and cut to about ½ in. (12 mm.) above the skin margin beforehand. The child is kept warm, and oxygen supplied if necessary. About 500 ml. of Rh-negative compatible blood is used, 20 ml. being removed and replaced at a time, the whole procedure taking 1 to 2 hours, during which 90 to 95% of the child's blood is replaced. The infant is given calcium [quantity and strength not stated] at the end of the operation to avoid possible alkalotic tetany from the large amounts of sodium citrate in the bottled blood. Penicillin and sulphadiazine are given prophylactically for 48 hours. A second transfusion was required in a quarter of the cases about 2 or 3 weeks later. One advantage of this method is that the child can be discharged from hospital with the mother.

Not every infant requires replacement transfusion. Only 1 in 8 babies sent to the author has required such treatment. The mother's blood is always examined to confirm that it contains anti-Rh agglutinins. If this is

so the case is assessed on the severity of the clinical findings—anaemia, jaundice, oedema, splenomegaly, and hepatomegaly. In addition Rh-positive babies, whose blood contains anti-Rh agglutinins and whose red cells are completely coated with antibody, develop severe symptoms on the second to fourth day, so that this laboratory finding alone is sufficient indication for replacement transfusion.

The author points out the difficulty of obtaining adequate control figures, since now cases are seen early and infants who would formerly have died arrive for treatment. Statistics collected over the past 15 years (all personally observed cases) show that before 1941 the mortality was 35 to 40%; between 1941 and 1945 this fell to 30%, possibly because of earlier diagnosis and improved treatment. Between 1943 and 1946 the mortality rate was 20%. The author hesitates to draw conclusions from cases treated in the last 15 months, but gives the following figures. A total of 95 cases was treated. Of these, 20 occurred in families in which a previous child had died of erythroblastosis, and these childrens' chance of survival is estimated at 1 in 10. In fact 70% survived. Of 85 of these infants transfused by the umbilical vein 65 are alive and well, their ages ranging from 3 to 15 months. Seven patients died of causes other than erythroblastosis; 7 died of the disease. Six infants showed kernicterus, and the author does not consider that this method prevents this complication.

A. T. Macqueen

2399. **Endogenous Creatinine Clearance of Infants Suffering from Exudative Diathesis.** [In English]
S. Zimányi. *Paediatria Danubiana* [*Paediat. danub.*] **4**, 262–267, Nov., 1948. 13 refs.

The endogenous creatinine clearance was measured in 12 infants and children aged from 2 to 32 months. All at the time of the measurement had skin lesions, such as intertrigo, seborrhoea of the scalp, and eczema, which are manifestations of the exudative diathesis. [The authors are, however, careful to point out that exudative diathesis is not a pathological or clinical entity.] The endogenous creatinine clearance in all subjects was decidedly lower than in normal subjects of the same age. On the basis of these findings it may be assumed that in these children there is a depression of the glomerular filtration rate; this may be due to a reduction in the total renal blood flow. The decrease in urine output noted by other authors in children exhibiting similar skin lesions may be due to the same cause. A true picture cannot, however, be obtained from investigating only a part of the renal function, and an increased tubular resorption cannot be excluded; the authors therefore intend to continue their work on this subject.

S. Doxiadis

2400. **Incidence of Diseases Among Reading Failures and Nonfailures**
T. H. Eames. *Journal of Pediatrics* [*J. Pediat.*] **33**, 614–617, Nov., 1948. 4 refs.

In the School of Education, Boston University, the author has investigated the incidence of physical disease in children who had difficulty in learning to read. Reading difficulty is sometimes hereditary and occurs more often in boys than girls. Very little is known of the pathology of the brain in these children. Previous investigators have approached the problem in different ways and it is probably true to say that there is no single cause. "Physical, emotional, psychological, social, and pedagogic components" must all be considered in the aetiology.

The occurrence of various groups of diseases in 875 children with reading failure is compared with that in a control group of 486. Speech defects and diseases of the mouth (excluding dental conditions), throat, nose, and ears were found more often in the reading-failure group than in the controls. Diseases of the eyes (excluding functional eye defects) and of the circulatory and urogenital systems also occurred more often than in the control group. Diseases of other systems were not found to a much greater extent in the reading-failure group than in the controls. It is stressed that the successful treatment of the child who cannot read depends on two factors, the correction where possible of physical defects, and an efficient method of instructing the child to the limit of his ability. *L. M. Rose*

2401. **Carbohydrate Metabolism of Atrophic Infants.** (Kohlehydratstoffwechsel atrophischer Säuglinge)
L. Barta and L. Gyengèsi. *Paediatria Danubiana* [*Paediat. danub.*] **4**, 246–250, Nov., 1948. 6 refs.

Double glucose-tolerance tests were performed on 12 infants suffering from chronic malnutrition. None had diarrhoea or fever when the tests were performed. In 9 of them the Staub effect—failure of the blood-sugar level to rise after the second dose—did not appear. The authors attribute the absence of the Staub effect to a disturbance of the intermediary carbohydrate metabolism during chronic malnutrition. *S. Doxiadis*

2402. **Carbohydrate Metabolism in Toxicoses of Infancy.** (Kohlehydratstoffwechsel bei Säuglingstoxikose)
L. Barta and L. Gyengési. *Paediatria Danubiana* [*Paediat. danub.*] **4**, 251–255, Nov., 1948. 4 refs.

The authors summarize their findings as follows: "The carbohydrate metabolism of atrophic infants suffering from toxicosis shows all the changes characteristic of atrophy. Glucose-tolerance tests carried out in eutrophic infants suffering from toxicosis result in irregular curves showing several peaks—in a small percentage of the cases the Staub effect may be absent. In infantile atrophy the changes in carbohydrate metabolism may be due to disturbed functioning of the liver cells while in toxicosis they might be ascribed to central regulatory dysfunction. Grave disorders of liver function could not be found in either atrophy or toxicosis."

[Both this and the preceding paper (Abstract 2401) are very short and in each case all the data are presented in one table. Because of the absence of sufficient information it is not possible to form an opinion on the validity of the authors' conclusions.] *S. Doxiadis*

Medicine: General

2403. **A Method of Testing Analgesics in Man**
A. J. H. HEWER and C. A. KEELE. *Lancet* [*Lancet*] **2**, 683–688, Oct. 30, 1948. 4 figs., 18 refs.

This paper describes the power of various analgesics to relieve pain experimentally induced in 4 healthy adults by the contraction of ischaemic muscle. After a preliminary rest of 5 to 10 minutes on a couch, a sphygmomanometer cuff was applied to the upper arm and inflated to 220 to 230 mm. Hg. The hand and forearm muscles were exercised by rhythmically compressing a sphygmomanometer bulb. After 50 or 60 contractions there was slight or moderate pain in the forearm muscles. The contractions were then stopped and the arm was rested with the ischaemia maintained. At first the pain decreased, sometimes disappearing altogether. After 1 to 3 minutes pain returned and increased steadily until, after 8 to 15 minutes, it became intolerable. On deflating the cuff the pain disappeared in a few seconds. With experience it was possible to distinguish various grades of intensity of pain from 1 to 10 units (1=very slight; 10=intolerable).

The drugs tested were injected intravenously when moderate pain (4 or 5 units) was present, and effective doses produced rapid but transient relief. The method of comparing the potency of the various drugs was to find the minimum dose which would reduce pain of 4 or 5 units' intensity. Morphine, " physeptone ", and " C.B. 11 " were equally active and about ten times as potent as pethidine. The inhalation of from 20 to 40% nitrous oxide in oxygen or air and of 3% cyclopropane in oxygen also relieved the ischaemic pain. Intravenous procaine relieved pain, its analgesic effect being mainly of central origin. Thiopentone, " benadryl ", " neoantergan ", " antistin ", and tetraethylammonium bromide have a recognized but weaker analgesic action. There was pronounced individual variation in response to the drugs used, and reactions differed considerably in their severity and nature. *Geoffrey McComas*

2404. **Cold Agglutinins (56 Observations).** (Les agglutinines froides. A propos de 56 cas observés)
E. BENHAMOU, B. M. ZERMATI, and A. ASSUS. *Annales de Médecine* [*Ann. Méd.*] **49**, 499–543, 1948. 1 fig., bibliography.

After a lengthy historical section, the authors define cold agglutination as the property of certain sera to agglutinate erythrocytes of all groups, including the subject's own corpuscles, at temperatures below that of the blood; agglutination is greatest when the temperature is 0° C. The temperature at which agglutination occurs is strictly proportional to the titre of the agglutinins. These cold agglutinins also act on leucocytes, platelets, and spermatozoa. Technical details of the detection and titration of cold agglutinins are given. The cases which the authors have studied fall into several groups and one full case report is given to illustrate each group. Cold agglutinins were detected in cases of acrocyanosis associated with haemolytic anaemia, of malaria, of cirrhosis of the liver, of Banti's syndrome, of recurrent fever, and of pregnancy, and after transfusions and the administration of sulphonamides. [It is unusual that no cases of atypical pneumonia are recorded.] The biological significance of cold agglutinins is discussed in some detail. The phenomenon is distinguished from pseudo-agglutination (rouleaux formation) and iso-agglutination. The authors discuss the nature of cold agglutinins and conclude that they are similar to true antibodies. Lastly, the authors examine the practical aspects of cold agglutination in relation to blood grouping and blood transfusion. *J. F. Delafresnaye*

ALLERGIC DISORDERS

2405. ***X*-ray Treatment of Asthma. Follow-up of 680 Cases.** (Traitement de l'asthma par la radiothérapie. (D'après une statistique de 680 cas suivis))
P. VALLERY-RADOT and P. BLAMOUTIER. *Presse Médicale* [*Pr. méd.*] **56**, 813–814, Nov. 20, 1948.

This paper is based on the study of cases of asthma and of paroxysmal rhinorrhoea observed over a period of 23 years. In all cases the condition had resisted usual forms of treatment. The authors point out that the course of asthma is so variable that it is difficult to assess accurately the results of treatment. Some cases were followed up for 10 years, others for less than 1 year, but the majority of cases were under observation for 2 years or more. Excellent results from *x*-ray therapy are claimed in 23% of cases, and there was marked improvement in 18% of cases, partial improvement in 23%, and failure in 36% of cases. The technique used is fully described. *J. F. Delafresnaye*

2406. **Protective Action of Combinations of Diphenhydramine and Aminophylline in Fatal Bronchospasm in Guinea Pigs due to Mecholyl Aerosol**
W. E. HAMBOURGER, H. B. FREESE, M. W. WINBURY, and P. M. MICHIELS. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **94**, 367–371, Dec., 1948. 1 fig., 6 refs.

According to some patients the respiratory symptoms after " mecholyl " injections more closely resemble those of asthma than do those produced by histamine. Usually all guinea-pigs die from bronchospasm after exposure to an aerosol of 2·4% mecholyl. Diphenhydramine (" benadryl ") and aminophylline injected intraperitoneally, separately or together (the admixture forms a milky suspension), give protection from this bronchospasm. The results indicate that both the protective and the

lethal effects of these two substances are additive. The action of 1 g. of diphenhydramine is equivalent to that of 3·22 or 2·17 g. of aminophylline for protection or intraperitoneal toxicity respectively. *Derek R. Wood*

2407. **The Heart in Bronchial Asthma**
M. K. HAJOS. *Annals of Allergy* [*Ann. Allergy*] **6**, 655–661, Nov.–Dec., 1948. 13 refs.

The circulatory system was investigated in 301 asthmatic patients, most of whom were between 16 and 45 years old. The systolic blood pressure varied from 120 to 80 mm. Hg in 48%; hypertension was found in 14%, mostly old people. *X*-ray examination showed a combination of small (" drop ") heart and emphysema in 14% of the cases. On electrocardiography right axis deviation was found in 44% and left axis deviation in 28%; depression of the ST segment and inverted T waves in leads II and III were frequent.
H. Herxheimer

2408. **Nethaphyl in Bronchial Asthma**
S. W. SIMON. *Annals of Allergy* [*Ann. Allergy*] **6**, 662–663 and 683, Nov.–Dec., 1948. 5 refs.

One " nethaphyl " tablet contains ¾ gr. (50 mg.) " nethamine " (methylethylaminophenylpropanol hydrochloride) and 2 gr. (0·13 g.) theophylline amino*iso*butanol. Nethamine is said to have a similar action to ephedrine. Nethaphyl with phenobarbitone was given to 40 patients suffering from intrinsic asthma; 35 of these preferred it to various combinations containing ephedrine. [No other data are given.] *H. Herxheimer*

2409. **Allergic Examination of Bakers and Millers.** [In English]
T. CASTBERG and C. M. SØRENSEN. *Acta Allergologica* [*Acta allergol., Kbh.*] **1**, 283–296, 1948. 1 fig., 26 refs.

The frequency of diseases due to flour allergy was investigated among 130 bakers and millers. Allergic symptoms when working with flour were reported by 42. In 14 asthma was the main complaint, in 13 vasomotor rhinitis; 8 had eczema, 6 urticaria, and 1 hemicrania. When intradermal skin tests were made on 93 of the 130 bakers, 39 gave positive reactions to flour or flour-improving substances, though only 26 of these had allergic symptoms. It is pointed out that ammonia persulphate, on account of its tendency to cause eczema, is not used in Denmark as an " improver ". *A. W. Frankland*

2410. **Blood Examinations in Hay Fever Patients during Acute Allergic Shock.** [In English]
T. CASTBERG and M. SCHWARTZ. *Acta Allergologica* [*Acta allergol., Kbh.*] **1**, 272–280, 1948. 29 refs.

Investigations were carried out on 5 hay-fever patients who developed a strong acute general allergic reaction similar to anaphylactic shock as it occurs in the guinea-pig. If the reaction is of short duration, with dyspnoea as the most pronounced symptom, leucopenia and a fall in blood-sugar level over a short period were observed. There was only a slight lowering of blood pressure. Investigation of the haemoglobin content, erythrocyte sedimentation rate, coagulation time, the serum chloride and bicarbonate and the fibrinogen contents, and the thrombocyte and eosinophil counts, showed insignificant variations. *A. W. Frankland*

2411. **The Significant Allergenic Air-borne Nonpathogenic Bacteria, their Incidence, Types of Allergies and Treatment. A Three-year Study**
P. SCHONWALD and E. F. DEPPE. *Annals of Allergy* [*Ann. Allergy*] **6**, 687–692, Nov.–Dec., 1948. 1 ref.

Petri dishes were exposed to the air in various positions in both town and country districts and a number of air-borne organisms cultivated. Some—such as *Micrococcus tetragenus* and *luteus*—were Gram-positive, some —*Pseudomonas aeruginosa*, for example—were Gram-negative, and some were spore-bearing bacteria, such as *Bacillus megatherium*, *mycoides*, and *subtilis*. Skin testing was done with a vaccine which contained 4,000,000 organisms per ml. Treatment was given to 155 patients, most of them suffering from asthma or rhinitis, and many of whom had been desensitized against pollen and other allergens without lasting success. After further desensitization with vaccine of air-borne bacteria 131 reported complete or at least moderate relief. The author includes 10 case histories. He concludes that this vaccine treatment is a reliable but slow remedy.
H. Herxheimer

METABOLIC DISORDERS

2412. **Heart and Circulation in Haemochromatosis.** (Herz und Kreislauf bei der Hämochromatose)
H. SCHULZE-BUSCHOFF, K. SPANG, and H. STOLLREITER. *Deutsches Archiv für Klinische Medizin* [*Dtsch. Arch. klin. Med.*] **193**, 416–433, 1948. 6 figs., 26 refs.

The authors give clinical records of 5 cases of cardiac complications in haemochromatosis, in 3 of which there was gross circulatory failure. Necropsies in 3 of the cases showed fibrosis of heart muscle in 2, due to deposits of iron pigment; in the other there was cardiac enlargement without valvular disease, but no histological examination was made. They emphasize that abnormal clinical signs in the heart and signs of gross circulatory insufficiency are uncommon. In 14 out of 15 cases, however, the electrocardiograms were abnormal. Any abnormality of rhythm or complexes may be found and there is no constant characteristic. Cardiac or circulatory insufficiency may be found only by more searching investigations than ordinary clinical methods—for example, shortened systolic times, 256 to 218 milliseconds, with slow pulse rates; small stroke volumes of 50 to 17 ml. per beat, which may even diminish on exertion in the same way as in normals; small resting minute volumes of 1·4 to 3·1 litres which increase on exertion but still remain well below normal exertion figures; and low blood pressures.

Briefly, patients with established haemochromatosis are liable to cardiac and circulatory insufficiency,

which may be due to structural changes or to chemical disturbances of function; in the majority of cases this will be discovered only by special investigations and will not produce overt clinical cardiac failure. *H. K. Goadby*

2413. **Adrenal Cortical Hormone Therapy of Malnutrition.** (Nebennierenrindenhormonbehandlung Unterernährter)
M. GÜLZOW. *Deutsches Archiv für Klinische Medizin* [*Dtsch. Arch. klin. Med.*] **193**, 465–480, 1948. 3 figs., bibliography.

Patients suffering from malnutrition were treated with " percorten " for brief periods during their nutritional therapy. Many blood estimations were made: red and white cell and platelet counts; haemoglobin, calcium, phosphorus, sugar, and protein values, residual nitrogen content, and blood volume; the basal metabolic rate was also determined. It is claimed that all abnormal values changed towards normal during the treatment and relapsed when it was stopped. The majority of such changes were clearly attributable to the salt and water retention and to the increase in plasma volume invariably noted; the platelet count increased and the abnormal albumin–globulin ratios in the plasma were corrected. If " large doses " of percorten were given after the patient had recovered by dieting, unpleasant reactions ensued, especially an increase of existing oedema. The reaction of patients with malnutrition to suprarenal cortical extract was the same as that in cases of Addison's disease.

[The number of cases and other details are not given, nor is the dosage of percorten stated.] *H. K. Goadby*

2414. **True and False Famine Osteopathies.** (Vraies et fausses ostéopathies de famine)
E. MARTIN and G. CHANAL. *Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften* [*Bull. schweiz. Akad. med. Wiss.*] **4**, 166–186, Sept., 1948. 3 figs., 12 refs.

" Famine osteopathy " is, in the opinion of the authors, often diagnosed on inadequate grounds. Osteopathies were seen quite frequently in clinics in Switzerland in wartime, in spite of good calcium and milk intake by the population, whereas they were rarely found at necropsy on large numbers of cases from German " extermination " camps (Uehlinger). Askanázy, and later Rutishauser, frequently found osteopathies in unselected post-mortem material. Osteopathies are ten times as common in women as in men. The authors postulate three main types of osteopathy: (1) fibro-osteoclasia, due to overaction of osteoclasts, and found in hyperparathyroidism, thyrotoxicosis, and renal disease; (2) osteomalacia, due to a mineralization defect curable by vitamin D, occurring in steatorrhoea, chronic jaundice, and sex-hormone defects; (3) osteoporosis, due to failure of normal osteoblastic stroma formation, and occurring in pituitary defects such as Cushing's syndrome, in pregnancy, and in conditions of defective protein intake. The causes of the osteopathy in any one case are often multiple. Biopsy of the bone of the iliac crest usually shows a mixture of the above three changes; it is a useful adjunct to history and ordinary physical examination and investigations, and may establish the possible causes of the abnormal skeletal condition. *H. K. Goadby*

2415. **Clinical and Pathological Studies in von Gierke's Disease.** (Studio clinico ed anatomopatologico sulla malattia di Gierke)
A. CHIEFFI and L. NASSI. *Rivista di Clinica Pediatrica* [*Riv. Clin. pediat.*] **46**, 631–696, Oct., 1948. 21 figs., bibliography.

From the Department of Paediatrics, Florence University, the authors report on 5 cases of von Gierke's disease, and advocate a new form of treatment with alcohol-benzol-acetone extracts of thymus gland (2 to 3 injections a week, each equivalent to 12 to 29 g. of fresh gland). Cases 1, 2, and 3 were studied pathologically in great detail; peculiar changes were found in the thymus, with diminution of acidophil cells in the anterior pituitary and changes in the pancreas (in case 1 suggesting hyperactivity of the islets, in cases 2 and 3 some degenerative changes). Case 4 was not studied adequately at post mortem. In case 3 the above-mentioned treatment was used with some benefit but the patient died of intercurrent diphtheria. In case 5, a typical case of von Gierke's disease in a 19-month-old boy, treatment with lipid-soluble thymus extract led to the following improvement: some decrease in liver size, abolition of hypoglycaemic crises, a return to normal of fasting blood-sugar levels, and a return to normal of the blood-sugar curve after injection of adrenaline.

After discussing extensively the literature and the views on the causes of this disease, the authors reject the theory that it may be due to accumulation of an abnormally resistant glycogen or to absence of a normal glycogen-splitting enzyme system. They think that the disease is the result of an abnormality of the endocrine glands. The pituitary gland is probably most implicated and there is an insufficient production of diabetogenic and growth-promoting hormone. This insufficiency may be secondary to a congenital hypothalamic lesion. They consider that under normal conditions the diabetogenic hormone of the anterior pituitary acts on carbohydrate metabolism through the thymus, which in its turn releases a specific hormone, probably of steroid structure. *P. E. Polani*

2416. **Studies on Beriberi in an Endemic Sub-tropical Area**
J. SALCEDO, E. O. CARRASCO, F. R. JOSE, and R. C. VALENZUELA. *Journal of Nutrition* [*J. Nutrit.*] **36**, 561–577, Nov. 10, 1948. 22 refs.

During an eight-month survey of beriberi in Bataan in the Philippines in 1947, 12,384 persons, comprising random samples (average 22·26%) of the population in each of 9 of the 12 municipalities, were examined. The presence of any of the following signs and symptoms was recorded by the examining physician: mouth—cyanosis, numbness of lips, tremor of tongue; gastro-intestinal—anorexia, vomiting, constipation, waist tightness; cardiovascular—fatigability, palpitation, tachycardia, murmurs,

enlarged heart, oedema; nervous system—tingling, numbness, reflex changes, paraesthesia; skin and muscles—pallor, tenderness (calf), cramps; in infants—ptosis, purposeless motions, opisthotonos, head-drop, aphonia. The clinical data were computed, following the classification used by Metcoff *et al.* (*J. Lab. clin. Med.*, 1945, **30**, 475) for their nutrition survey in Newfoundland, thus: (1) frank or apparent beriberi—3 characteristic signs, or 2 signs and 1 or more symptoms; (2) suggestive beriberi—2 signs, or 1 sign and 1 or more symptoms; (3) clinically doubtful beriberi—1 sign or signs less definite.

The incidence of clinically diagnosed beriberi, in relation to the various physiological groups examined, was found to be highest in expectant mothers, next in nursing mothers, " other adults ", infants, and children; in relation to the total population of the community, the highest incidence of beriberi was in " other adults ", followed by nursing mothers, then by expectant mothers, children, and infants. In all, 1,580 cases of " clinical " beriberi were found, representing 12·76% of the population; with frank beriberi 1·99%, suggestive beriberi 3·58%, and doubtful beriberi 7·24%. It was noted that the reported mortality from beriberi was highest in infants and next in " other adults ", there being no deaths of expectant mothers and only a very small number among nursing mothers; the low incidence in infants compared with the high mortality (140·1 per 100,000 population for 1947) is a reflection of the rapidity of fatal termination of beriberi in infants. In addition to physical examination, determinations were made of the " fasting-hour " urinary excretion of aneurin after a 12-hour overnight fast in all the beriberi cases and, for comparison, in 65 apparently normal subjects; the authors conclude that the determination cannot be diagnostic by itself but that, in conjunction with clinical signs and symptoms, a low excretion of aneurin (from 0 to 2 μg.) in the " fasting-hour " urine specimen could be helpful in the diagnosis of beriberi.

It was noted that washed rice is predominantly the daily food in the Philippines. *Joseph Parness*

2417. **The Genetics of Gout and Hyperuricemia—An Analysis of Nineteen Families.**
C. J. Smyth, C. W. Cotterman, and R. H. Freyberg. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 749–759, Nov., 1948. 3 figs., 19 refs.

In this article the hypothesis is discussed and investigated that gout is caused by a dominant autosomal gene [the gene placed on any chromosome other than the XY or sex chromosome] expressing itself fairly regularly in hyperuricaemia but only occasionally in gouty arthritis. An analysis is given of 19 gouty families. In each case the original patient was a male with clinical, biochemical, and in most cases radiological evidence of gouty arthritis. Altogether 87 relatives were studied. The variation in serum urate levels was studied by general statistical methods in order to ascertain whether the relatives could be divided into " normal " and " hyperuricaemic " groups, in the hope that these would correspond to two specific genotypes.

Despite important individual variations, the frequency diagrams suggested a bimodal distribution of serum urate levels among relatives of both sexes, who were therefore classified on the basis of the minimum points in these distributions—namely, males with over 6 mg. of uric acid per 100 ml. of serum, and females with over 5 mg., were considered hyperuricaemic. The females averaged 1 mg. less uric acid than males—a finding which agrees with that of previous workers. The statistical evidence also appeared to show that males under 16 years of age did not under any circumstances have serum urate levels above 6 mg. If it was assumed that the metabolic change resulting in hyperuricaemia is not manifested in males till about the age of puberty, the data concerning the male relatives was in agreement with the hypothesis of dominant autosomal inheritance. The proportion of hyperuricaemic females was, however, significantly smaller than that expected. It is therefore probable that hyperuricaemia is not detectable in some heterozygous females even when a liberal reduction in the critical level for hyperuricaemia is made.

Although gouty arthritis occurs much more frequently in males than in females, the evidence does not suggest the existence of sex-linkage. This is made unlikely by the common occurrence of gouty or hyperuricaemic sons of gouty male patients. With sex-linkage one would also expect higher average urate levels, or a higher incidence of hyperuricaemia, among daughters of hyperuricaemic males than among daughters of hyperuricaemic females. [The results recorded give no suggestion of such a difference.] *R. P. Foggie*

2418. **A Study of Tests of Liver Function in Diabetes and of the Antidiabetic Value of Lipotropic Factors.** (Contribution à l'étude des tests hépatiques au cours du diabète et de la valeur antidiabétique des facteurs lipotropes)
P. A. Bastenie, K. Kowalewski, and S. Rutman. *Acta Gastro-Enterologica Belgica* [*Acta gastro-ent. belg.*] **11**, 369–385, Aug.–Sept.–Oct., 1948. 1 fig., 32 refs.

In 15 unselected cases of diabetes mellitus many tests of liver function were performed: cephalin-flocculation, Takata, blood-cadmium, hippuric-acid, and quantitative van den Bergh tests; estimations of total blood fats and cholesterol, total plasma protein, albumin–globulin ratio, and urinary urobilin concentration. In all but the protein concentrations abnormal figures were found in all patients; there was no difference between the fat and the thin type of patient. Ten out of the 15 patients were then given daily 1·125 g. of methionine, 750 mg. of choline chloride, 375 mg. of inositol—a mixture of substances known to be synergistic in preventing or reducing an abnormally high fat content in the liver. The other 5 cases served as controls. All cases were re-examined after 6 and after 12 weeks, and in those receiving the " lipotropic " treatment the results of the liver function tests improved: in 8 out of the 10 cases the diabetes was also improved, as shown by lowered insulin requirements. In the 5 control cases no changes in the results of the tests were found. The importance of controlling the fat metabolism in prevention of degenerative diseases in diabetes is emphasized. *H. K. Goadby*

Cardiovascular Disorders

2419. **The Insensible Loss of Water in Congestive Heart Failure**
C. J. D'ALTON, R. C. DARLING, and E. SHEA. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 516–522, Nov., 1948. 29 refs.

No difference was found in the amount of water lost through the skin in patients with and without cardiac oedema. It is evident that hydrostatic pressure plays no part in the passage of water vapour through the skin.
C. W. C. Bain

2420. **The Movement of the Mitral Ring in Cases of Pathologic Changes in the Left Ventricle Especially within the Posterior Papillary Muscles.** [In English]
H. ODQVIST. *Acta Radiologica* [*Acta radiol., Stockh.*] **30**, 182–190, 1948. 9 figs., 5 refs.

The author has made a cineradiographic study of a case showing calcification of the mitral ring. He stresses that no comparison can be made with the findings of other workers in this field unless the location of the calcification is identical and the projections used are similar. Calcifications of the mitral ring should be readily distinguishable from those of the aortic ring by noting that the former lie to the left of the spine in the postero-anterior view, and in the posterior part of the heart in the second oblique projection. The aortic ring, on the other hand, is superimposed over the spine in the postero-anterior view, and in the second oblique projection is seen to lie in the middle of the heart. The author found that the locus of movement of the mitral ring in his case was triangular, there being a pull downwards and to the left at the end of systole. Post-mortem analysis of the heart showed fibrosis due to old infarctions of the posterior wall and posterior papillary muscles of the left ventricle. He concludes that this incoordination of the mitral valve flaps was responsible for the triangular form of the movement. Information is thus obtainable during life of the presence of localized lesions affecting the papillary muscles. *A. M. Rackow*

2421. **Abnormal Rapid Rhythms Associated with Digitoxin Therapy**
H. D. LEVINE. *Annals of Internal Medicine* [*Ann. intern. Med.*] **29**, 822–837, Nov., 1948. 8 figs., 33 refs.

The occurrence of abnormal rhythms in 7 patients who received digitoxin at the Peter Bent Brigham Hospital, Boston, led to a study of the incidence of such rhythms when digitalis leaf and digitoxin were used. Out of 534 who received digitalis leaf 2 developed tachycardia certainly due to digitalis and 3 a tachycardia possibly due to digitalis. Out of 338 who received digitoxin 7 developed tachycardia certainly due to digitoxin (3 due to overdosage, 3 not due to excessive dosage, and 1 possibly due to excessive dosage). Idioventricular rhythm, ventricular tachycardia, and auriculo-ventricular dissociation are regarded as rhythms generically similar and including that of digitalis intoxication. Such abnormal rhythms also develop with *Digitalis purpurea* and *Digitalis lanata*, but the clinical impression is that because digitoxin causes little nausea and vomiting it produces intoxication more insidiously. It is recognized that intoxication may be an expression of overdosage but it may be due to some unknown cardiac factor even when ordinary doses are used. A rising heart rate may be due to incipient intoxication as well as to progressive heart disease, and a sudden change from an irregular to a regular rhythm also suggests intoxication. The authors make it clear that the purpose of their observations is to exhort to greater vigilance and not to deprecate the use of digitoxin. *John Anderson*

2422. **The Heart in the Terminal State: Effect of Intracardiac Epinephrine**
E. MASSIE, C. H. HUGULEY, and H. S. STILLERMAN. *Annals of Internal Medicine* [*Ann. intern. Med.*] **29**, 838–859, Nov., 1948. 11 figs., 16 refs.

Animal experiments have drawn attention to the possibility of revival of organisms, and in particular to the possible effect of intracardiac therapy on the dying heart. A review is given of the literature of electrocardiography of the dying heart and also of resuscitation of the heart which has stopped beating. The latter suggests that the effects of intracardiac injection of drugs may be non-specific and due to mechanical stimulation.

The electrocardiographic changes before death, at death, and after death were studied in 34 cases, and the effects of intracardiac and intramyocardial adrenaline were also studied. A great variety of rapidly shifting arrhythmias and changes in rate was recorded. Slowing of the heart was almost constant, with sino-auricular nodal depression, and auriculo-ventricular nodal rhythm in about a third of the cases. Auriculo-ventricular and intraventricular blocks were common and evidences of ventricular irritability were also very common—fibrillation, flutter, premature contractions, and bizarre terminal complexes. Auricular fibrillation occurred only when established before death.

In 7 out of 18 cases a response to adrenaline (epinephrine) was noted. In 5 of these the injection was thought to be intramyocardial. In 2 it was intracardial. In only 2 was a significant restoration of ventricular rhythm found, and in 5 merely fibrillation and ventricular premature beats. On the basis of these experiments it is suggested that intramyocardial injection of adrenaline is more valuable than intracardiac injection and that injections given before complete cardiac arrest should be more effective than after cardiac arrest. *John Anderson*

2423. **Massive Hypertrophy of the Heart with Special Reference to Bernheim's Syndrome.**
L. R. EVANS and P. D. WHITE. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 485–491, Nov., 1948. 9 figs.

In 1910 and 1915 Bernheim published his view that a hypertrophied left ventricle by partial occlusion of the right ventricular chamber could produce the signs of right ventricular failure, namely, distension of the neck veins and injection of the facial veins, with cyanosis, oedema of the lower limb, and congestion of the liver in the absence of pulmonary congestion.

The authors, working at the Massachusetts General Hospital, and believing this syndrome to have a somewhat uncertain foundation, have studied the clinical and necropsy records in 33 cases of massive hypertrophy of the heart to at least twice the normal weight. Of these 33, 22 showed left ventricular hypertrophy. Four points were studied: (1) the initial symptoms of heart failure; (2) the weight of the liver and the lungs; (3) hearts with a left ventricular myocardium at least twice as thick as the right; (4) right auricular enlargement in the *x*-ray films. On the grounds of history alone no case was acceptable as one of Bernheim's syndrome. Comparison of the weights of the liver and lungs failed to suggest any evidence of Bernheim's syndrome, neither was gross eccentric hypertrophy of the left ventricle found to be associated with the symptoms expected. Finally, right auricular dilatation was not seen in the *x*-ray films.

The authors sum up by saying that they could find no clear-cut evidence of Bernheim's syndrome in their material. They consider it to be an unlikely entity on theoretical grounds, and criticize recorded cases on the grounds that actual pulmonary embolism and pulmonary hypertension were not sufficiently considered as causes of right ventricular failure. *John Anderson*

2424. **Isometric Relaxation Period of the Left Ventricle in Normal Subjects and Patients with Mitral Stenosis**
A. A. LUISADA, F. J. ROMANO, and J. M. TORRE. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 23–26, Oct., 1948. 3 figs., 10 refs.

This paper analyses the heart sounds, comparisons being made between the normal subject and patients with various clinical conditions. The authors consider the problem of distinguishing between the split second sound due to a variety of causes and the true reduplication of this sound from loud snapping of the mitral leaflets in mitral stenosis. They suggest that the actual length of the period of isometric relaxation of the left ventricle, being the interval between the closure of the aortic and the opening of the mitral valves, is important in this connexion. From the study of a large number of normal subjects with the phonocardiogram it was found that the opening of the healthy mitral valves could in a few cases be isolated, and therefore the period of isometric relaxation of the left ventricle be measured. Parallel studies were made of patients with mitral stenosis. The length of this period in normal subjects varied between 0·04 and 0·07 second, while in the patients with mitral stenosis it was between 0·07 and 0·11 second and revealed the typical prolongation of the isometric relaxation period in this condition. Simultaneous phonocardiographic and fluorocardiographic recordings showed the isometric relaxation period to lie on the fluorocardiogram between the lowest point of the ventricular wave and the beginning of the diastolic rebound.

Cases in which a split second sound without mitral stenosis was present, as well as subjects with a third heart sound, were also studied. The period between the two phases of the split second sound averaged 0·04 second, and between the second and third sounds the average time was 0·15 second. *R. P. Foggie*

2425. **Production of Experimental Heart Failure in Dogs with Intact Circulation**
A. ROOS and J. R. SMITH. *American Journal of Physiology* [*Amer. J. Physiol.*] **153**, 558–566, June, 1948. 1 fig., 28 refs.

Heart failure was produced in dogs by injection into the left ventricle of a 3·3% suspension of potato starch in saline, the aorta being occluded immediately above the heart for a few seconds during the injection. This produced diffuse myocardial damage by coronary embolism, most of the injected small (diameter 12 to 72 μ) particles presumably getting into the coronary arteries. The injections were repeated at 2 to 7 minute intervals. After more than three injections myocardial failure was produced in most dogs, as evidenced first by a progressive rise in right auricular pressure, then by dilatation of the heart, congestion of the lungs and liver, and pulmonary oedema. The arterial pressure did not fall significantly until congestive heart failure had fully developed. The experiments usually terminated in death. Congestive failure could generally be produced with less starch suspension when the blood volume was first increased by 100 to 250 ml. of blood. In a few animals congestive heart failure did not develop but a precipitous fall in arterial blood pressure occurred, leading to death.

It is noted that whereas in the experiments of Landis *et al.* coronary ligation alone (without "exercise") produced a fall in venous pressure, coronary embolism in the present experiments produced a progressive rise in pressure. There is a discussion on the changes in cardiac output in relation to right auricular pressure.
H. Pollak

2426. **Renal and Circulatory Factors in the Edema Formation of Congestive Heart Failure**
A. P. BRIGGS, D. M. FOWELL, W. F. HAMILTON, J. W. REMINGTON, N. C. WHEELER, and J. A. WINSLOW. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 810–817, Nov., 1948. 3 figs., 25 refs.

Twenty-one cases of congestive heart failure were extensively studied and compared with 18 cases of heart disease without failure. In 10 of the cases with failure it was possible to repeat the studies after compensation had

been restored. The glomerular filtration rate was found to be decreased in the cases of failure, but it did not always increase significantly as the oedema disappeared, whereas the ability to excrete sodium invariably increased. The authors conclude that some factor connected with the heart failure is present which forces the kidney to resorb sodium and water more completely than normal. Of the circulatory measurements the only one that showed a fairly consistent difference between the two groups was the oxygen saturation of the mixed venous blood. In most instances this was lower in the uncompensated cases and improved with compensation. The authors suggest that this indicates cellular hypoxia, which, acting possibly through the posterior pituitary or the suprarenals, causes the kidney to resorb sodium and water more completely with resultant oedema formation. Once oedema is established, increased capillary hydrostatic pressure and lowered plasma protein level may maintain or perhaps increase it. *B. McArdle*

2427. **The Effect of Intravenous Procaine on the Electrocardiogram of the Dog**
M. H. Uhley and M. Wilburne. *American Heart Journal* [*Amer. Heart J.*] **36**, 576–581, Oct., 1948. 4 figs., 24 refs.

Electrocardiographic changes were studied in dogs after intravenous injection of procaine-hydrochloride (50 mg. per kilo body weight). The dogs were first anaesthetized with pentobarbital sodium. Only lead II was recorded. The predominant changes in the electrocardiogram were the prolongation of the P–R interval and the alterations in the QRS complex. The extent of these changes was closely correlated with the rate of injection. Other changes noted were: (1) alterations in heart rate; (2) increase in amplitude of P; (3) reduction in amplitude of QRS, with a deep S wave; (4) increase in amplitude of T independent of heart rate. In one instance a " chaotic " heart action with multiple ectopic pacemakers was produced. From these findings it is deduced that, in addition to a powerful depressant action on the conduction system of the heart, procaine has also an effect upon the myocardium—" some alteration in the depolarization and repolarization patterns ". It is suggested that the changes in heart rate are due to both cardiogenic and reflex factors. Attention is drawn to the obvious correlation between the chaotic cardiac action caused by the rapid intravenous injection of procaine and the human fatalities which have been recorded after intravenous use of procaine. *William A. R. Thomson*

2428. **The Effects of the Cardiac Glycosides upon the Dynamics of the Circulation in Congestive Heart Failure. I. Ouabain**
R. A. Bloomfield, B. Rapoport, J. P. Milnor, W. K. Long, J. G. Mebane, and L. B. Ellis. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 588–599, Sept., 1948. 8 figs., 18 refs.

The object of this study was, by means of certain newer techniques, to gain further insight into the action of ouabain. Thirteen patients with heart disease, with and without clinical evidence of congestive heart failure, were investigated. Ouabain was injected through an intracardiac catheter into the right ventricle or pulmonary artery, over a period of one to two minutes, in doses of 0·25 to 0·75 mg. and the cardiac output was estimated before and afterwards by the direct Fick method. Intracardiac, femoral arterial, and peripheral venous pressures were optically recorded, the zero level for pressures in the peripheral veins and lesser circuit being taken as 5 cm. below the angle of Louis.

In general it is believed that ouabain has an action on the circulation that is qualitatively similar to that of the digitalis glycosides, and that it differs from these quantitatively in its rapidity of action and its rapid elimination, and in that it is not absorbed from the alimentary tract. Some authorities also consider it has less effect on the sinus node and junctional tissues, but a greater action on the cardiac muscle itself, than digitalis preparations.

The authors' main conclusions were that the cardiac output was increased in heart failure owing to the fact that ouabain causes an increase in the stroke volume, and that this greater stroke volume could best be explained by a direct action on the contractility of the myocardium. The systemic and right-heart pressure changes found were consistent with such an explanation, although vasopressor effects of the drug were not entirely excluded. Actually, in 3 patients the cardiac output was unchanged or fell as a result of injections of ouabain, but 2 of these were not suffering from clinical heart failure. *S. Oram*

2429. **An Estimation of the Hepatic Blood Flow and Splanchnic Oxygen Consumption in Heart Failure**
J. D. Myers and J. B. Hickam. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 620–627, Sept., 1948. 4 figs., 10 refs.

Catheterization of the hepatic veins has provided a means of estimating the hepatic blood flow and splanchnic oxygen consumption in man. The cardiac output can be measured by taking samples from the right heart by partially withdrawing the catheter.

Thirteen patients with heart failure of various degrees, and from different causes, but each with a low cardiac output, were studied and the results were compared with those obtained from 14 subjects with no significant disease. Usually the catheter entered one of the right hepatic veins, and the liver blood-flow was estimated by the bromsulphalein method. It was found that the estimated hepatic blood-flow varied over a considerable range in both the control and the heart-failure groups, and it was considered that this was due to the fact that the flow through only one portion of the liver was being determined, and that the flow as estimated from several areas of the same liver under the same conditions may show considerable variation. The hepatic blood-flow for patients with heart failure ranged from 200 to 800 ml. per minute per sq. metre of body surface, with a mean of 535 ± 170 ml. The controls gave values of 600 to 1,160 ml. per minute per sq. metre, with a mean of 850 ± 170 ml. The difference in the average values was statistically significant. The decrease in hepatic blood flow was roughly proportional to the decrease in the

total cardiac output. The liver received its usual percentage of the total output, in this respect differing strikingly from the kidney, which undergoes a great and disproportionate reduction in blood flow. The reduction in liver blood flow was compensated by an increase in hepatic arterio-venous oxygen difference so as to provide, under conditions of rest and fasting, a normal splanchnic oxygen consumption. *S. Oram*

2430. **The Use of Acetylcholine in the Objective Determination of Circulation Time in Man**
J. C. SCHLICHTER, M. WILBURNE, and M. GROSSMAN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 523–527, Nov., 1948. 1 fig., 13 refs.

Acetylcholine has been used in doses of 10 to 60 mg. to determine the arm-to-heart circulation time. An electrocardiogram taken simultaneously with the intravenous injection gives the end-point by a failure of an auricular or ventricular complex to appear on time. The usual initial dose was 20 mg., which was increased by increments of 10 mg. if no response was observed. The normal circulation time by this method varied from 1·2 to 6 seconds; the highest recorded time was 16 seconds. Out of 58 injections, 46 were successful. Two patients developed auricular fibrillation some 20 seconds after the injection, and quinidine was required to restore normal rhythm; others had asystole lasting up to 3·8 seconds.

The authors suggest that the method is simple and accurate, but that it cannot, however, be regarded as entirely free from risk. *C. W. C. Bain*

2431. **Intracardiac Potentials Recorded by Cardiac Catheterization in Man.** (Les potentiels intra-cardiaques recueillis par cathétérisme chez l'homme)
P. W. DUCHOSAL, C. FERRERO, J. P. DORET, P. ANDEREGGEN and B. RILLIET. *Cardiologia* [*Cardiologia, Basel*] **13**, 113–128, 1948. 17 figs., 12 refs.

Intracardiac electrocardiograms were registered by means of a cardiac catheter from positions in the right auricle, right ventricle, and (once) left auricle. The tracings were registered simultaneously with the three standard leads, and either the right arm or the central terminal was used for the distant electrode. Investigations were carried out on 1 normal subject and 19 sufferers from cardiac disorder. Employment of the central terminal or right arm caused differences in voltage but not in shape of the endocardial tracing. Comparatively small changes in position of the intracardiac electrode caused very considerable changes in the resultant tracing. Large P and small QRS waves were registered from the auricles, and small P and large QRS waves from the ventricles. Ectopic beats were caused by the passage of the electrode into the right ventricle. In cases of right bundle-branch block, the expected delay in the R wave was found with the electrode inside the right ventricle. In the same case rapid onset of negativity was found with an extrasystole, apparently arising in the right ventricle. [For further details the illustrations accompanying the paper should be consulted.] *G. Schoenewald*

2432. **Determination of the Levo- and Dextrocardiogram**
M. SEGERS. *American Heart Journal* [*Amer. Heart J.*] **36**, 751–756, Nov., 1948. 4 figs., 6 refs.

Working on the assumption that the laevo- and dextrocardiograms can be determined from the electrocardiograms of incomplete bundle-branch block, the author describes a method of calculating this in cases in which the block is transient and normal complexes can also be recorded. The normal and abnormal complexes are recorded on the same tracing in leads I, II, III, and CR_5. The time that elapses between the beginning of the earliest QRS wave in any one limb lead and the moment at which the intrinsic deflection occurs in lead CR_5 is measured in the normal and abnormal electrocardiogram. The difference between the two values represents the delay in left ventricular activation in the case of incomplete bundle-branch block. From the figures and equations which are provided the laevo- and dextro-cardiograms are calculated. From data obtained in 11 cases of transient incomplete bundle-branch block it is concluded that the normal laevo- and dextro-cardiograms cannot be considered as mirror images with opposite axis orientation; they are very similar to a normal bicardiogram but of lower amplitude. The main difference between them is that in leads I and II the laevocardiogram shows a QR and the dextrocardiogram an RS deflection.
William A. R. Thomson

2433. **Penicillin Treatment of Subacute Bacterial Endocarditis. Report of Eighteen Consecutive Cases**
A. C. HERRING and W. M. DAVIS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 726–730, Nov. 6, 1948. 1 fig., 18 refs.

Results of treatment with penicillin in 18 cases of subacute bacterial endocarditis are given with detailed reports of 2 of them. Penicillin was administered by continuous intravenous or intramuscular drip for about 4 weeks, the dose ranging from 200,000 to 500,000 units daily, but the dosage in relapsed cases was much higher. It is thought, however, that better results can be obtained with higher doses in all cases, at least 2,000,000 units daily for 6 weeks being recommended. When the sensitivity of the organism *in vitro* is greater than 0·06 unit of penicillin per ml. the daily dose should be 5,000,000 units or more at the onset.

Of the 18 treated patients, 10 were alive and had been well over a period of one year or more. Seven died; of these, 2 were inadequately treated because of shortage of penicillin; 1 died in a first attack of subacute bacterial endocarditis and 1 in a relapse; in the 3 others the infection had been arrested. The infection was controlled in 75% of the cases, and 25% proved resistant to therapy. One patient was successfully treated, and again responded during a relapse 20 months later; for this last the daily dose of penicillin was 5,000,000 units for 37 days. In one patient treatment failed despite the administration of streptomycin and of over 1,000,000,000 units of penicillin, with a daily dose reaching at one time 20,000,000 units and the maintenance of blood penicillin levels well above the concomitant organism sensitivity. The organism

was of the resistant type described by Loewe as *Streptococcus* " s.b.e." *S. H. Cookson*

2434. **Disappearance of Bundle Branch Block After Duration of Twelve Years**
J. FREUNDLICH. *Experimental Medicine and Surgery* [*Exp. Med. Surg.*] **6**, 406–415, Nov., 1948. 5 figs., 12 refs.

The return to normal of a long established bundle-branch block is apparently an unusual observation. Two cases of bundle-branch block of 12 and 3 years' duration respectively are reported in which the QRS abnormality disappeared after the intravenous administration of " aminophylline " and mercurial diuretics. The first patient had in addition complete A-V block, and sinus rhythm was restored with treatment. The changes towards normal in the E.C.G. appearances were noted *pari passu* with clinical improvement. The author expresses the view that the abnormalities in ventricular conduction should be ascribed to " myocardial fatigue ", myocardial ischaemia conditioned by coronary artery disease, and oedema of the myocardium. The last factor can be eliminated by administration of mercurial diuretics, aminophylline, and ouabain.
A. I. Suchett-Kaye

2435. **The Effect of Posture Upon Axis Deviation in Human Bundle Branch Block**
A. M. JONES and H. FEIL. *American Heart Journal* [*Amer. Heart J.*] **36**, 739–750, Nov., 1948. 6 figs., 15 refs.

Stimulated by a case of bundle-branch block in which serial standard limb lead electrocardiograms taken over a period of eighteen months showed marked changes in axis deviation, and in which it was found that these changes could be produced by altering the posture of the patient, the authors have investigated the effect of posture in 20 cases of right bundle-branch block and 20 cases of left bundle-branch block. Standard limb leads, Goldberger's augmented unipolar limb leads, and precordial leads were used. The three positions of the patient studied were the supine and the right and left lateral. In 8 of the cases of left bundle-branch block the axis shifted more than 30 degrees on moving from the supine to the lateral position, and in 6 of these the shift of axis exceeded 60 degrees; the greatest shift was 185 degrees. With one exception the shift of axis was to the right. In 4 of the cases of left bundle-branch block the side of the block was reversed, as judged by standard limb leads, on adoption of the lateral posture. The results in the cases of right bundle-branch block were not so striking: there was a shift of axis of more than 30 degrees in 7 cases, but in no case did the standard limb lead electrocardiogram simulate the appearance of left bundle-branch block, nor was the electrical position of the heart ever grossly altered.

The practical conclusion is reached that these results " indicate once again the importance of a standard posture in recording the electrocardiogram, provide yet another example of the fallacy of attributing significance to the axis deviation as an indication of the side of bundle branch block, and emphasize the reliability of adequate praecordial leads in deciding this point ".
William A. R. Thomson

2436. **Pulmonary Stenosis without Septal Defect**
A. A. POLLACK, B. E. TAYLOR, H. M. ODEL, and H. B. BURCHELL. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **23**, 516–520, Oct. 27, 1948. 1 fig., 6 refs.

Congenital pulmonary stenosis without septal defect is rare. Three cases are reported, with widely differing clinical pictures, in which catheterization studies established this diagnosis. *J. L. Lovibond*

2437. **Renal Function Before and After Surgical Resection of Coarctation of the Aorta**
J. GENEST, E. V. NEWMAN, A. A. KATTUS, B. SINCLAIR-SMITH, and A. GENECIN. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **83**, 429–438, Nov., 1948. 2 figs., 30 refs.

Twelve out of 17 patients suffering from coarctation of the aorta were investigated before and after operation to determine the renal filtration rate, the renal plasma flow, and the filtration fraction. In most of the cases the successful resection of the constriction and the end-to-end anastomosis produced an increase in the renal blood flow and a decrease of the filtration fraction. The authors believe that the diminished renal blood flow with nearly normal filtration rate in patients with coarctation of the aorta is due to a compensatory efferent arteriolar constriction—a physiological mechanism similar to that present in essential hypertension. The successful operation of the coarctation releases the constriction of the efferent artery. *A. I. Suchett-Kaye*

2438. **Physiological Studies in Congenital Heart Disease. VI. Adaptations to Anoxia in Congenital Heart Disease with Cyanosis**
R. J. BING, L. D. VANDAM, J. C. HANDELSMAN, J. A. CAMPBELL, R. SPENCER, and H. E. GRISWOLD. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **83**, 439–456, Nov., 1948. 4 figs., 20 refs.

The physiological mechanism of adaptation to anoxaemia in congenital heart diseases with cyanosis was studied, and the results are discussed with reference to changes operating in anoxaemia of high altitudes. The investigation was carried out in 35 patients with the tetralogy of Fallot. While at high altitude the anoxaemia is the result of decreased partial pressure of oxygen in the inspired air, in the cyanotic group of congenital cardiac abnormality the cause of anoxaemia is a reduction in the effective pulmonary blood flow due to right-to-left intracardiac shunt. The following points were considered: (1) The effect of hyperventilation; this is an important factor at high altitude, but in the patients studied the presence of the intracardiac shunt nullified the effect of hyperventilation. (2) Decrease of the basal metabolic rate in tetralogy of Fallot, which can be

reversed by a successful Blalock operation. (3) Adjustment of the acid–base balance—an adjustment to anoxaemia more effective in the patients studied than in normal individuals. (4) The oxygen dissociation curve and the increase in the oxygen-carrying capacity of the blood. *A. I. Suchett-Kaye*

2439. **Familial Interauricular Septal Defect wtih Mitral Stenosis (Lutembacher's Syndrome)**
S. R. COURTER, B. FELSON, and J. MCGUIRE. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 501–508, Nov., 1948. 2 figs., 33 refs.

Two sisters aged 21 and 25 years with Lutembacher's syndrome are reported; no previous report of this syndrome in brothers or sisters has been found in the literature up to 1947. Uncomplicated interauricular septal defects in siblings have not been reported and the authors believe this to be the first report of such an occurrence. Fifty-four cases of Lutembacher's syndrome have been reported in the literature.

The history and physical findings in these 2 cases are described and radiographs, electrocardiograms, and phonocardiograms reproduced. Criteria for the diagnosis are mentioned, namely, possible retardation of mental and physical growth, enlargement of the left praecordium, evidence of increased intrapulmonary pressure in an accentuated or split pulmonary second sound, a systolic murmur in the first and second left interspaces to the left of the sternum, and occasionally a basal diastolic murmur (relative pulmonary insufficiency). Fluoroscopy should show signs of: (1) generalized enlargement of the right heart; (2) marked prominence of the pulmonary conus; (3) increased hilar markings with "hilar dance"; (4) a small left ventricle; (5) a hypoplastic aorta. To these signs are added a characteristic apical diastolic murmur to complete the findings in the syndrome. The blood pressure is commonly low (100/70 and 90/70 mm. Hg in these 2 cases). Differential diagnosis is from an atypical patent ductus arteriosus, associated with a high pulse pressure and a prominent pulsating aorta and balanced ventricular hypertrophy; from Eisenmenger's complex in which cyanosis is permanent; and from acquired pulmonary artery dilatation and chronic cor pulmonale. *John Anderson*

2440. **The Prognosis in Myocardial Infarction. I. The Prognosis After the Acute Stage. Study of 100 Cases.** (La prognosi dell'infarto miocardico. I. La prognosi dell'infarto miocardico dopo il periodo acuto. Studio di 100 casi)
A. MUSSAFIA and V. MASINI. *Cuore e Circolazione* [*Cuore e Circol.*] **32**, 193–200, Aug., 1948. 3 figs., 13 refs.

A series of 100 patients who survived the acute stage of myocardial infarction was followed up. The patients could be divided into three groups: (*a*) Those who made a good functional recovery, without angina or cardiac failure. There were 3 women and 54 men in this group, and the ages ranged from 30 to 72 years, with an average of 50 years. In 32 patients hypertension, and in 25 angina, preceded the attacks. Five of the patients died, a new infarct being the cause in 4. (*b*) Those who suffered from angina following the infarct. In this group were 22 men and 1 woman; the ages ranged from 34 to 72 years, with an average of 49·5 years. Hypertension preceded the infarction in 15 cases, angina in 18 (in 10 associated with hypertension), and cardiac failure in 1 (associated with hypertension). Four patients died while under observation, a further infarct being the cause of death of 2 of them. (*c*) Patients with subsequent cardiac failure. In this group there were 2 women and 18 men, whose ages ranged from 48 to 65 years, with an average of 56·3 years. Hypertension preceded the attack in 16 patients, angina in 10 (of which 9 had associated hypertension), and cardiac failure in 7 (all associated with hypertension). Seven patients subsequently died of cardiac failure, but none had a further infarction during the period of observation.

Many patients survived the original infarction for more than 8 years. Causes of death were cardiac failure or coronary insufficiency (usually a further infarction). Cardiac failure was more common when hypertension preceded infarction. Recurrence of infarction was unpredictable, and occurred in patients of the first group many years after the first attack. *F. A. Langley*

2441. **The Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort**
W. B. PORTER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 509–515, Nov., 1948. 4 figs., 12 refs.

Four patients with angina pectoris and normal electrocardiograms at rest developed frequent premature ventricular systoles immediately following an exercise test. After treatment with quinidine, 0·3 g. thrice daily, the effort tolerance increased and no premature systoles occurred during the exercise test. Two of the 4 patients died soon afterwards, and it is suggested that premature systoles occurring during the tachycardia induced by exercise have a grave prognostic significance. Since death is probably due to ventricular fibrillation in these patients, it seems reasonable to give them quinidine.
C. W. C. Bain

2442. **Methylthiouracil in the Treatment of Congestive Heart Failure and Angina Pectoris. Results of Prolonged Treatment.** [In English]
A. R. FRISK and I. LINDGREN. *Acta Medica Scandinavica* [*Acta med. scand.*] **132**, 69–90, Nov. 15, 1948. 2 figs., 13 refs.

A report is given of treatment of 7 cases of mitral valvular disease and 9 cases of angina pectoris with methylthiouracil.

The authors class results in 3 of the 7 cases of mitral disease as successes [but, as these cases were treated in hospital by rest in bed and administration of digitalis and mercurial diuretics in unstated dosage, as well as by methylthiouracil, it is difficult for the reader to form an opinion of the results]. In the first case pulmonary congestion and dyspnoea were stated to be the only indica-

tions of failure and these were improved. In the second case, decompensation is said to have been present [but no mention is made of any enlargement of the liver or of peripheral oedema]. In this case also the condition is stated to have been improved. The fourth patient suffered from attacks of paroxysmal auricular fibrillation, and these attacks ceased for some months under treatment with methylthiouracil, but then recurred. The condition is stated to have been improved and the improvement to have been maintained for 8 months after the withdrawal of methylthiouracil [a fact which seems to make it doubtful whether the original improvement was due to this drug]. The sixth patient, classed as "severely decompensated", had dyspnoea, tachycardia, and basal pulmonary rales; the condition was "considerably improved" after 6 months. [No figures of respiratory or cardiac rate are given.] The seventh patient had an enlarged liver, ascites, pleural transudate, and peripheral oedema; she was "considerably improved and able to walk about" [but no statement is made about the extent to which these features cleared up].

In contrast, a description of 9 cases of angina pectoris reveals unequivocal improvement in 8 cases as measured by improved ability for physical effort checked by ergometric measurements and ability to tolerate anoxaemia induced by breathing oxygen-deficient air.

G. Schoenewald

2443. **An Evaluation of Esophageal Electrocardiograms in the Diagnosis of Healed Posterior Myocardial Infarction** H. B. BURCHELL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 492–500, Nov., 1948. 7 figs., 11 refs.

The correct interpretation of the initial downward ventricular deflection (Q_3) in lead III is difficult. Statistical methods have group value but no real individual usefulness in assessing the meaning of Q_3. Somewhat more useful has been the employment of the augmented unipolar extremity lead (aVF) but the problem remains. Oesophageal lead electrocardiography has been suggested as an aid to diagnosis of posterior infarction and to the elucidation of the Q_3 pattern in the standard leads.

The present study from the Mayo Clinic is based on 50 patients, 18 with acute myocardial infarction; 9 of these showed late Q_2 T_2 Q_3 T_3 changes diagnostic of posterior infarction; 13 had angina pectoris without evident myocardial infarction and 19 had no clinical evidence of coronary artery disease, but, of these 19, 16 had a deep Q_3 wave and 3 a deeply inverted T_3 wave. The technique of oesophageal electrocardiography is simple but interpretation of patterns is difficult because the exact position of the lead cannot be easily determined and because this uncertainty leads to confusion between the forms at atrial levels when posterior myocardial infarction exists (the forms are closely similar). It is also unfortunate that the transitional zone between atrial and infra-atrial leads is very variable. It is made clear from this study that the specific problem, the significance of a deep Q_3 wave (when it is an isolated finding), is not solved by the use of oesophageal leads. Nor does it appear that any significant advantage is to be gained at present by the use of this lead when the standard leads and lead aVF are not helpful. [It is furthermore unfortunate that in such a study no pathological correlation was obtained.]

John Anderson

2444. **Studies of Fluorocardiography: Tracings of the Left Ventricle in Myocardial Infarction.** [In English] A. A. LUISADA and F. G. FLEISCHNER. *Acta Cardiologica* [*Acta cardiol., Brux.*] **3**, 308–327, 1948. 11 figs., 23 refs.

Fluorocardiography is a photoelectric method of recording movement of a cardiac (or great vessel) silhouette. The object is to record pulsation, but movement caused by change of position of the heart as a whole is of course also recorded. Briefly the method is as follows. With the patient in a fluoroscopic stand, a small area of the cardiac profile is selected for investigation, and opposite this area a photoelectric tube with a slit is applied to the screen so that the slit is at right-angles to the cardiac contour. With movement of the opaque heart the amount of light from the screen which enters the phototube will vary, and with it the current emitted by the tube. This current is fed to an electrocardiograph which records a curve. Other channels of the cardiograph are used for a simultaneous phonocardiogram and, if required, a pulse tracing. Elaborate arrangements are necessary to eliminate interference from the *x*-ray equipment, and these are described. The results of the method in 20 patients with old and recent cardiac infarction are described. The fluorocardiograms, when compared with the normal, showed an aberrant form both in systole and in diastole, the main observation being a reduction and absence or inversion of the movement in systole.

The site of the dynamic changes was in close correlation with the site of myocardial damage indicated by the electrocardiogram, but it is suggested that the former may more accurately show the extent of the damage, particularly when there are multiple cardiac infarctions.

[The method seems to deserve intensive application in the study of heart movements, both in cardiac infarction and in other heart diseases.]

S. H. Cookson

BLOOD VESSELS

2445. **Modification of Katz's Method in the Treatment of Obliterating Vascular Lesions of the Limbs.** [El método de Katz, modificado, en el tratamiento de las lesiones vasculares obliterantes de los miembros) F. BASCH. *Prensa Médica Argentina* [*Prensa méd. argent.*] **35**, 1641–1645, Aug. 20, 1948.

Katz's method (*N. Orleans med. surg. J.*, 1946, **98**, 542) consists of bi-daily intravenous injections of 10% of anaesthetic ether in physiological serum. The present author has used initially a suspension of 10 ml. of ether in 20 ml. of serum injected once daily, but found that the veins at the site of the injections became quickly sclerosed, so he changed to a 20% suspension. Six cases of advanced and crippling arteritis obliterans were treated by 8 to 20 daily injections. As a result the pain either

disappeared or decreased, and peripheral circulation improved, causing the disappearance of oedema and rapid healing of inflammatory lesions where they existed. Intermittent claudication subsided in one case and became less frequent in others. A disadvantage of the injections is a transient but acute pain along the injected vessels.

A. Lilker

2446. **Thrombo-Angiitis Obliterans. Results of Sympathectomy and Prognosis**

J. B. KINMONTH. *Lancet* [*Lancet*] **2**, 717–719, Nov. 6, 1948. 4 figs., 1 ref.

This is an excellent analysis of the clinical features and results of treatment in 77 patients with thrombo-angiitis obliterans. Oscillometry is recommended in oedematous limbs when swelling makes it difficult to feel the pulse. Histological examination of the arteries is likely to give misleading results unless an adequate length of vessel is sectioned, for the damage may only be patchy. Thrombosis of superficial veins was the first symptom of the disease in 25% of cases. Buerger's disease is episodic and many patients were found to have had remissions lasting for up to 10 years or more. Without a very long follow-up study, therefore, it is impossible to assess the effect of treatment accurately. The natural course of the disease extends over several decades. Three clinical types of Buerger's disease are recognized, that in which there is obstruction of a main artery, that in which there is obstruction of small vessels, and that in which both large and small vessels are involved. Lumbar ganglionectomy gave greatest relief where the small vessels were alone involved. The prognosis was much less favourable where a main artery was blocked: in the " combined " type it was poor and appeared not to be improved by sympathectomy.

Francis F. Rundle

2447. **A New Treatment for the Relief of Obliterative Diseases of Peripheral Arteries**

I. MUFSON. *Annals of Internal Medicine* [*Ann. intern. Med.*] **29**, 903–913, Nov., 1948. 5 figs., 5 refs.

The procedure described is an important advance in the treatment and relief of obliterative diseases of peripheral arteries. The author observes that many simple measures will give temporary relief, and much depends on the development of a competent collateral circulation. Sympathectomy is widely practised, but it has its limitations in the arteriosclerotic group. Also, sympathectomy is of doubtful value as a lasting measure and cannot be repeated for relapses.

The method here described is the injection into the femoral artery, by an ingenious technique, of 500 ml. of normal saline to which is added between 1·38 and 2·75 mg. of histamine acid phosphate, equivalent respectively to 0·5 and 1 mg. of histamine base. This injection is given weekly or even twice weekly, and the results are recorded of treatment of 500 patients without mishap, complication, or difficulty. The improvement was assessed partly by clinical judgment, partly by measurement of temperature of the treated limb, and particularly by tracing the improved vascular bed by means of radiosodium. The clinical improvement was estimated by the number of " blocks " of city buildings around which the patients could walk without pain after treatment as compared with the number before treatment, and also the number of hours they could lie in bed without being awakened by pain.

[There can be no doubt that the story of this work will be greeted with considerable enthusiasm everywhere, and not least in Britain, but for details of the technical procedures the original paper should be consulted.]

G. F. Walker

2448. **Further Experience with Sex Hormones and New Investigations with Dihydroergotamine and " Percorten " in Treatment of Disturbances of Peripheral Circulation.** (Weitere Erfahrungen mit Sexualhormonen sowie neue Untersuchungen mit Dihydroergotamin und Percorten zur Behandlung peripherer Durchblutungsstörungen)

R. NÄF. *Praxis* [*Praxis*] **37**, 503–509, July 8, 1948. 3 figs., 20 refs.

The author investigated 99 patients suffering from circulatory disturbances, These comprised: cold hands and feet, 28; chilblains, 34; acrocyanosis, 27; erythrocyanosis crurum puellarum, 3; " dead finger ", 4; Raynaud's disease, 2; and Buerger's disease, 1. The rate at which the extremities recovered their warmth after chilling was measured before and after treatment. The hands were placed for 10 minutes in water at 45° C., then for 10 minutes in water at 15° C., after which they were dried without friction, and the skin temperature was measured with a thermocouple during the succeeding 21 minutes. The temperature curve was charted against time, and the area enclosed by the curve was measured planimetrically. The figures thereby obtained before treatment were compared with those obtained after, and also with those from normal individuals. Women outnumbered men by 64 to 35; of the 43 women of reproductive age, there was evidence in 22 of some minor endocrine dyscrasia (mainly menstrual troubles). Of the 99 patients, in 73 the return of warmth to the skin was delayed. The drugs tried were: testosterone, oestradiol dipropionate, progesterone, " fenocyclin ", adrenocortical extract, desoxycorticosterone acetate, and dihydroergotamine, each in various preparations. Of 54 patients treated, 10 were cured, 33 improved, and 11 unaffected. Recommendations are made as to the type of drug and dosage to be used for the various age groups in either sex.

Bernard Freedman

HYPERTENSION

2449. **Paroxysmal Hypertension Associated with Tabes Dorsalis. Report of Three Cases**

I. L. BENNETT and A. HEYMAN. *American Journal of Medicine* [*Amer. J. Med.*] **5**, 729–735, Nov., 1948. 4 figs., 20 refs.

The association of paroxysmal hypertension with tabes dorsalis has received little attention but is important because by its recognition needless surgical exploration

of the adrenals may be avoided. References to some 22 cases in the literature are listed, and the authors report 3 more cases in detail. Previous reports have stressed the association of sudden rises in arterial pressure with gastric crises, but these were present in only one of the authors' patients. In this instance, the attacks were painless and accompanied only by nausea and vomiting. In the second patient, the hypertension was entirely asymptomatic, and in the third the arterial paroxysms were symptomless except for occasional association with lightning pains. Penicillin treatment benefited the hypertensive crises in the first patient, but not in the other 2 patients. The periods of hypertension may or may not be associated with symptoms, and the authors attribute them to disturbances of the autonomic nervous system.

T. Anwyl-Davies

2450. **The Causation of Acute Arterial Necrosis in Hypertensive Disease**

F. B. Byrom and L. F. Dodson. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 357–368, July, 1948. 4 figs., 19 refs.

In this paper the authors attempt to answer three questions: (1) Is hypertension a link in the chain of causation that leads to the necrotizing arteritis seen in cases of malignant hypertension? (2) If it is, what is the mechanism? (3) Are any of the links dependent on renal dysfunction or destruction?

From their own work and that of others they conclude that the absence of necrotizing arteritis in a kidney of which the artery is partially compressed, that is, the kidney protected from the experimentally produced hypertension, points to an affirmative answer to the first question. The mechanism is described by them as a sudden hydraulic overstrain of the arterial wall, with consequent necrosis and lysis of the overstretched muscle, and they detail the results of producing brief overdistension of the arterial tree in normal rats by intracarotid injection of Ringer's solution. One kidney was protected by constriction of the renal artery; the other showed muscular necrosis of the arcuate and interlobular arteries and of the afferent glomerular vessels.

To the third question they provide a less certain reply and, although admitting that failure of renal excretion or absorption of the products of dead renal tissue may be able to play a part in causing some forms of necrotizing arteritis in experimental animals, they none the less obviously favour the purely mechanical causation in the human subject.

A. C. Lendrum

2451. **The Effect of Sodium Chloride Depletion on Blood Pressure and Tetraethylammonium Chloride Response in Hypertension**

W. W. Stead, M. F. Reiser, S. Rapoport, and E. B. Ferris. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 766–777, Nov., 1948. 6 figs., 29 refs.

A standard dose of 400 mg. of tetraethylammonium chloride (TEAC) was given intravenously to patients with hypertension, and the resulting fall in blood pressure was measured. On the assumption that all autonomic ganglia were blocked, the fall in blood pressure was regarded as representing the loss of the neurogenic component, and the remaining pressure as representing a humoral component.

In a group of 12 unselected hypertensive patients the effect of TEAC on the blood pressure during a control period, a period of salt depletion, and a period when salt was again given was studied. During salt depletion 5 patients with moderate renal impairment showed a lowered residual blood pressure after administration of TEAC. In 4 of these the blood pressure before giving TEAC was unaltered by salt depletion. There were no consistent changes in serum sodium levels. Of 7 patients who had either malignant hypertension or renal failure with uraemia, or both, none showed change in blood pressure or in response to TEAC. In these cases the serum sodium levels fell from 15 to 20 mg. per litre.

It is suggested that in some hypertensive patients with only moderate renal impairment sodium depletion lessens the humoral component of the increased peripheral resistance, while in other patients with malignant hypertension or renal failure, or both, the humoral component of the peripheral resistance is not so affected.

D. Verel

2452. **The Relation of Vascular Disease to the Hypertensive State. II. The Adequacy of the Renal Biopsy as Determined from a Study of 500 Patients**

B. Castleman and R. H. Smithwick. *New England Journal of Medicine* [*New Engl. J. Med.*] **239**, 729–732, Nov. 11, 1948. 2 figs., 4 refs.

Examination of kidney biopsy material from a further 500 cases has confirmed the authors' previous findings—namely, that in a considerable proportion of patients suffering from hypertension (45·6%) there are either no renal vascular changes or such slight changes as to make it unlikely that they persisted and caused hypertension. The percentage distribution of slight, moderate, and marked renal vascular changes in these 500 cases approximated closely to the figures obtained in the authors' first series of 100 cases (*J. Amer. med. Ass.*, 1943, **121**, 1256).

G. Schoenewald

2453. **The Use of Dibenamine in Pheochromocytoma. Report of a Case**

H. C. Spear and D. Griswold. *New England Journal of Medicine* [*New Engl. J. Med.*] **239**, 736–739, Nov. 11, 1948. 7 figs., 3 refs.

The adrenolytic properties of "dibenamine hydrochloride", given as an intravenous infusion of 7 mg. of the drug per kilo body weight diluted in 300 ml. of 5% glucose in saline, were used to confirm the diagnosis of adrenal phaeochromocytoma. The patient had many daily episodes of paroxysmal hypertension and reacted with a particularly severe paroxysm to 0·05 mg. of histamine intravenously. After intravenous infusion of dibenamine these attacks ceased for 72 hours, and during this period histamine injections failed to produce hypertension. The diagnosis was confirmed at operation when the tumour was successfully removed.

G. Schoenewald

Disorders of the Blood

2454. **Puncture Biopsy of the Liver in Haematology.** (La ponction-biopsie du foie en pathologie sanguine)
P. CAZAL. *Sang* [*Sang*] **19**, 664–675, 1948. 13 figs.

Detailed descriptions are given of the histology of the liver in various blood dyscrasias, all the specimens having been obtained by puncture. [There is nothing specifically new in the paper but it is an excellent summary of the diagnostic value of the procedure.] *A. Piney*

2455. **A Method for Studying the Effect of Various Substances Upon Red Cell Maturation *in vitro***
E. E. HAYS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 528–533, Nov., 1948. 19 refs.

In the method described use is made of erythrocytes from the femoral marrow of adult male rats weighing from 140 to 180 g. The animal is killed, marrow is aspirated and centrifuged twice, the immature cells on top are suspended, and the solution to be tested is added. The whole is incubated at 38° C. for 36 hours. Thereafter 1,000 cells are counted and the number of mature reticulocytes per 1,000 cells is calculated. Details of the technique are given, the results being expressed in terms of the reciprocal of the amount of the unknown substance required to produce the same result as is obtained from 0·01 μg. per ml. of the standard liver extract.

By this method it was found that neither synthetic *Lactobacillus casei* factor nor vitamin Bc conjugate caused marked maturation while normal human and rat sera did. Serum from a patient with pernicious anaemia in relapse did not affect the maturation process (Hays, *Proc. Soc. exp. Biol., N.Y.*, 1946, **63**, 558). The effect on maturation of other substances was tested; glutathione, L-tyrosine and "bacto-yeast" extract had some effect on maturation of erythrocytes. *J. B. Wilson*

2456. **Mechanisms of Leukopenia with Inflammation. An Additional Leukopenic Factor Found in Alkaline Exudates**
V. MENKIN. *Archives of Pathology* [*Arch. Path.*] **46**, 145–158, Aug., 1948. 3 figs., 19 refs.

At Temple School of Medicine, Philadelphia, 1·5 ml. of turpentine was injected into the pleural cavity of dogs. The alkaline 24-hour exudate was one-third saturated with ammonium sulphate and centrifuged, the supernatant fluid being dialysed till free of sulphate, half saturated with ammonium sulphate, and left overnight, or longer, on ice. The supernatant fluid was then centrifuged. The precipitate usually contained a new leucopenic factor to be called "leucopenin". The supernatant fluid was dialysed until free of sulphate and contained a polypeptide leucocytosis-promoting factor (L.P.F.) This when lyophilized and frozen as a fairly thin film on a glass container will keep at room temperature in a desiccator. After some months it becomes inactive and insoluble in isotonic sodium chloride solution (in which state it is injected into dogs' hearts to cause leucocytosis). If the aged L.P.F. is centrifuged the supernatant fluid if found to contain active L.P.F. and the precipitate (denatured α_1 and α_2 globulins) contains "leucopenin" and a little L.P.F.

If "leucopenin" is hydrolysed by decinormal hydrochloric acid, the product produces leucocytosis only. The previously reported leucopenic factor is found in acid exudates associated with "pyrexin", from which it may be dissociated by decinormal hydrochloric acid. If exudate at *p*H 7·2 to 7·5 is injected, leucopenia occurs in one hour, followed by leucocytosis. This leucopenia (in dogs) averages 23·5%. On heating the exudate to boiling point and repeating the experiment, the leucopenia averages only 15·5%. With an exudate of *p*H 6 to 6·2 the initial fall is 23·5% and after heating it is 39%.

The author deduces that alkaline exudate has two leucopenic factors, thermolabile "leucopenin" and thermostable leucopenic factor; in the acid exudate there is a little "leucopenin" and much of the other leucopenic factor (*Arch. Path.*, 1946, **41**, 50), and heating in acid inactivates L.P.F. Chemical analysis shows a slight increase in sulphur as the only difference between the precipitates of fresh and aging L.P.F. None of the substances mentioned is present in normal serum. Similar responses can be obtained with human serum. With "leucopenin" the leucopenia produced mostly affects monocytes and lymphocytes. *Peter Harvey*

2457. **Paroxysmal Cold Hemoglobinurias**
R. M. BECKER. *Archives of Internal Medicine* [*Arch. intern. Med.*] **81**, 630–648, May, 1948. 35 refs.

This is a review of 37 cases of syphilitic paroxysmal haemoglobinuria, with a discussion of the difference between this condition and cold haemoglobinuria not associated with syphilis. In syphilitic cases the haemolysin becomes fixed to the red cells in the cold, and is activated in the presence of complement only when the blood is again warmed. The Donath–Landsteiner test illustrates this *in vitro*. In paroxysmal cold haemoglobinuria there is a high titre of cold agglutinins, which causes haemolysis on exposure to cold alone. Cold agglutinins are usually present in a titre of over 1 in 3,000. In the syphilitic type positive blood Wassermann and Kahn reactions are essential for diagnosis, and the presence of complement is necessary for haemolysis. In this type, again, a dermolysin can be demonstrated, although its effect can be minimized by the administration of antihistamine drugs. No dermolysin is demonstrable in the serum of patients with cold haemoglobinuria. Urticaria is therefore seen only in the syphilitic type of disease. In syphilis the haemolysin is type-specific, whereas the cold agglutinins act on all types of blood as

well as on the blood of other animals. Antisyphilitic treatment results in cure or amelioration of the condition in most cases of syphilitic paroxysmal cold haemoglobinuria. A case in which a successful response was obtained to treatment with penicillin is presented in detail. *Alan Kekwick*

2458. **The Haematopoietic System.** (Le système hématopoïétique)
F. MAS MAGRO. *Sang* [*Sang*] **19**, 617–636, 1948. 10 figs.

A detailed study is given of intra-vitam staining of haematopoietic tissues, mainly of the guinea-pig, which should be read in the original. The most important observations are concerned with the alleged directive activity of the histiocytic system, to which is attributed a power of changing the *p*H of the tissues and so affecting the course of cellular differentiation. Thus, the author refers to the haematopoietic tissues as possessing also a hormonopoietic function. A secretion of lymphatic tissue is alleged to stimulate the formation of lymphocytes while inhibiting myelopoiesis [cf. Miller, Herbut, and Jones, *Blood*, 1947, **2**, 15, who discuss the treatment of acute leukaemia on similar lines]. *A. Piney*

ANAEMIAS

2459. **Intravenous Iron Therapy.** (Le traitement intraveineux par le fer)
G. HEMMELER. *Acta Medica Scandinavica* [*Acta med. scand.*] **132**, 364–377, 1949. 5 figs., 15 refs.

The author records his experience with intravenous iron therapy. His observations were made both on patients and on rabbits. He concluded that iron given intravenously stimulates erythropoiesis to a greater extent than does iron given by mouth. Since the body is unable to excrete iron not needed for haemoglobin synthesis he believes that it should only be given intravenously to patients with hyposiderosis. This form of treatment is particularly valuable for patients who are unable to absorb iron from the gastro-intestinal tract or who for some reason do not tolerate it. He comments on the toxic effects seen if ferrous or ferric salts are given and himself uses a preparation called "ferronascine", in which the iron is in the form of sodium ferric di-(α,γ-dihydroxy-β,β-dimethyl) butyrate. The dose is 120 mg. daily. He believes that any complex salt which ionizes slowly can be used successfully since the iron then combines with the proteins of the serum.
Janet Vaughan

2460. **Cryptogenic Erythrocyte Metabolism.** (Der kryptogene Erythrocytenumsatz)
L. HEILMEYER and T. EILERS. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 975–976, Oct. 9, 1948. 1 fig.

In certain types of anaemia (Addisonian anaemia and those due to malignant tumours, infections, or lymphogranuloma) the amount of urobilin substances excreted seems to be greater than can be accounted for by calculation of the degree of anaemia and the rate of formation of erythrocytes. One of the authors (Heilmeyer) attempted to ascertain whether a supplementary new formation of erythrocytes occurred which was not detectable by the usual methods (reticulocyte count). The other author has detected other reticulocytes—very pale in colour and visible only in blood films immersed for 8 to 12 hours in Giemsa's stain after previous staining with brilliant cresyl blue and fixation in methyl alcohol. In comparison with normal erythrocytes these cells have a very short life (24 to 48 hours); they are of defective structure and are rapidly destroyed, especially in the spleen. These pathological erythrocytes disappear rapidly when pernicious anaemia is treated with liver extract or when remission of anaemia of infective or lymphogranulomatous origin occurs.
G. Hemmeler (*Excerpta Medica*)

2461. **Acute Anaemia. Iron Treatment or Not.** (Acute anaemier. Jernbehandling eller ikke)
V. ORAM. *Ugeskrift for Laeger* [*Ugeskr. Laeg.*] **110**, 1217–1219, Oct. 21, 1948. 2 figs., 7 refs.

To determine whether iron is necessary in the treatment of cases of acute anaemia following haemorrhage, the author plotted the rate of rise in the haemoglobin level in patients admitted to Sönderborg Hospital after abortion. Of such patients admitted between 1922 and 1945, 275 received iron and 312 did not. The author found that the rise in the haemoglobin level was above the mean in 64% of cases in the former group, whereas this was so in only 56·1% of the latter group. The rise in the haemoglobin level in untreated cases ranged from 2 to 28% at the end of 40 days, while in treated cases it ranged from 3 to 48%.

Between the 10th and 40th days the contrast between the two groups was more marked; in 49·4% of the treated cases the haemoglobin level was above the mean for the whole series, but this was true in only 31·8% of the untreated cases. The author concludes that in the majority of cases the blood picture can be restored from the patient's own depots of iron; if, however, the anaemia persists after the 10th day further investigations should be carried out to determine the cause of the delay.
B. Nordin

2462. **Pernicious Anaemia in Malnutrition.** (Perniziöse Anämie bei Mangelernährung)
U. HÄNEL. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 1101–1104, Nov. 13, 1948. 27 refs.

A marked increase in the number of cases of pernicious anaemia occurring in Germany under conditions of malnutrition has been noted. Some of the 220 cases observed were considered to be cases of nutritional macrocytic anaemia. Hyperchromic anaemias thought to have an alimentary basis have been described as occurring in infants fed on a goat's milk diet, and Wilhelmij of Holland has noted an increase in the average cell diameter of erythrocytes in subjects who were losing weight

during the war. The differential diagnosis and the differences in pathogenesis are described. The clinical findings, in the 220 cases examined, were those of a true cryptogenic pernicious anaemia, some cases behaving like those of true alimentary type by not reacting to purified liver extracts. It is therefore concluded that, besides the anti-pernicious anaemia principle other factors found in animal proteins are involved; these are identical with the active principle the absence of which is responsible for the occurrence of alimentary macrocytic anaemia. A diet deficient in animal protein is cited as a cause for the frequent occurrence of true pernicious anaemia. *Harold Jarvis*

2463. **Action of Thymine in Pernicious Anaemia.** (Zur Thyminwirkung bei Anaemia perniciosa)
H. E. Bock. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 1104–1106, Nov. 13, 1948. 2 figs., 19 refs.

The beneficial action of the pyrimidine derivative, thymine, on the megaloblastic bone marrow in pernicious anaemia was confirmed. A daily dose of 10 to 20 g. by mouth produced rapid, but not excessive, reticulocyte crises. Deterioration in the form of a spinal cord degeneration, frequently mentioned in the literature, occurred only in 1 case out of 8 under observation. Thymine is therefore suitable for short-term treatment provided the nervous system is kept under careful observation. The methyl radicle in the fifth position on the pyrimidine ring is of great importance as regards anti-anaemic action. Thymine is 2 : 6-dihydroxy-5-methylpyrimidine. 4-Methyl-2 : 6-dihydroxypyrimidine, administered in daily doses of 15 g. by mouth, did not produce any maturation of the bone marrow or a satisfactory increase in the number of reticulocytes. There was even a decrease in the number of leucocytes and erythrocytes in the peripheral blood and a fall in the cellular content of the bone marrow. Further observations will be required before this can be attributed to an anti-thymine effect. *Harold Jarvis*

2464. **Thymine, Folic Acid, and Vitamin B_{12} in Nutritional Macrocytic Anaemia, Tropical Sprue, and Pernicious Anaemia**
T. D. Spies, R. E. Stone, G. G. Lopez, F. Milanes, R. L. Toca, and T. Aramburu. *Lancet* [*Lancet*] **2**, 519–522, Oct. 2, 1948. 4 figs., 3 refs.

The authors report in detail the case histories of 3 patients, each suffering from megalocytic anaemia of different aetiology—nutritional anaemia, tropical sprue, and pernicious anaemia. Each patient relapsed and was admitted to hospital on three separate occasions, and the treatment during the three periods in hospital forms the basis of comparative studies of the efficacy of thymine, folic acid, and vitamin B_{12}. In each instance, after the total blood count, red cell volume, and icterus index had been determined, the patients were maintained on meat-free diets. During the first period in hospital each patient received 6,000,000 μg. thymine daily by mouth, and during the second period 10,000 μg. folic acid daily by mouth; in the third period the 3 patients received a single intramuscular injection respectively of 6μg., 23 μg., and 15 μg. of vitamin B_{12}. Each of the drugs caused a satisfactory improvement in the blood picture in all 3 cases, but, weight for weight, vitamin B_{12} was by far the most effective anti-anaemic substance tried. *H. Payling Wright*

2465. **Studies on the Cytometric Reduction of Erythroblasts in Pernicious Anaemia During Treatment with Liver Extract.** (Ricerche sulla riduzione citometrica degli eritroblasti dell'anemia perniciosa in corso di trattamento epatico)
G. Astaldi and V. Gallo. *Minerva Medica* [*Minerva med., Torino*] **2**, 308–315, Oct. 6, 1948. 8 figs.

Like Ferrata, the authors believe that megaloblasts are derived directly from histio-endothelial cells, that the normoblasts are derived from haemocytoblasts, and that the pro-erythroblast does not exist as a common stem cell for all types of erythropoiesis. Under the influence of liver treatment megaloblastic marrow rapidly undergoes normoblastic transformation. Megaloblastic erythropoiesis ceases and basophilic megaloblasts mature into normoblasts, but haemoglobinized megaloblasts still develop into megalocytes. While the marrow becomes transformed intermediate cell types occur.

In a patient with advanced pernicious anaemia the cell and nuclear diameters were estimated in sternal-marrow smears before and after 18, 58, and 76 hours of liver therapy. The " cytoplasmic " diameters were calculated. Individual graphs were drawn for basophilic, polychromatic, and orthochromatic erythroblasts regardless of whether they were megaloblasts or normoblasts. Both nuclear and cytoplasmic diameters of all cell types rapidly fell. The distribution curves for all diameters were at first flat, but later became more compact and showed a preponderance of the larger cells. *E. Neumark*

2466. **Skin Tests for Sensitivity to Liver**
P. C. Reynell. *British Medical Journal* [*Brit. med. J.*] **2**, 784, Oct. 30, 1948. 5 refs.

In an attempt to assess the value of skin tests in the recognition of sensitivity to injections of liver extracts, 11 patients receiving maintenance parenteral liver therapy were compared with the same number of patients, of similar age and sex distribution, suffering from other disease, in their local reactions to 0·05 ml. of liver extract injected intradermally. Definite wheals were produced in 9 patients in each group, and neither group showed any significant difference in the extent or intensity of the wheals. When patients from the two groups were tested with varying dilutions of liver extract, it was found that 8 out of 14 reacted to a dilution of 1 in 10, 1 out of 26 reacted to a dilution of 1 in 100; and none (out of 17) to a dilution of 1 in 1,000. Three other patients with clinical manifestations of acquired sensitivity to liver, however, all reacted with definite whealing to a dilution of 1 in 100 and 2 of them to a dilution of 1 in 1,000. It is concluded that most normal people respond with a

typical wheal and flare to the intradermal injection of undiluted liver extract, and that such reactions are of no diagnostic significance. The use of dilutions of purified extract of 1 in 100 or more may, however, be of considerable diagnostic value, especially in patients with vague and indefinite symptoms after injections of liver extract.

L. J. Davis

2467. **Neurological Sequelae in Macrocytic Anemia of Gastrointestinal Origin Following Folic Acid Therapy**
L. M. MEYER. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **18**, 811–814, Oct., 1948. 1 fig., 12 refs.

A case of nutritional macrocytic anaemia is reported in which neurological manifestations developed during folic acid therapy. The patient was a male aged 35 in whom a macrocytic anaemia was first diagnosed 19 years previously; at that time he was believed to be suffering also from ulcerative colitis. He was treated successfully for many years with oral or parenteral liver therapy, but at the age of 29 he was operated on for regional ileitis, the terminal ileum and ascending colon being removed. Subsequently his anaemia relapsed and he passed several bulky fatty stools daily. After further liver therapy he developed sensitivity reactions to liver given parenterally. Oral therapy with liver, "ventriculin", and yeast was ineffective. He was maintained on blood transfusions for 4 years, when folic acid therapy was started. The haematological and clinical responses were excellent, but after 13 months he complained of paraesthesiae, and 6 months later showed definite evidence of peripheral neuritis and dysfunction of the postero-lateral spinal tracts. At this time radiological evidence of regional ileitis was demonstrated, and free hydrochloric acid was found in the gastric juice after histamine. The patient was then desensitized and intensive parenteral liver therapy resumed. This was followed by a normal blood picture and by the disappearance of neurological abnormalities.

L. J. Davis

2468. **Paths of Circulation of Haematopoietic Substances and Their Excretion in Urine.** (Пути циркуляции гемопоэтических веществ и выделение их в моче)
O. B. MAKAREVICH. Архив Патологии [*Arkh. Patol.*] **10**, No. 4, 21–26, 1948. 16 refs.

In the first instance blood from the stomach veins was examined for the presence of anti-anaemic factor. Blood of cats was taken from the vena gastro-lienalis after ligation of the vessels of the spleen. Rats then received injections of 1·5 to 2 ml. of the blood serum. No reticulocyte reaction was observed. The same results were obtained with blood serum from the portal vein of the cat. The author concluded that either the concentration of haematopoietic substances in the blood is too low for detection with the test adopted or that haematopoietic substances are present in the blood in an inactive form, perhaps even together with specific inactivators.

The author then showed in 14 out of 18 experiments that gastric juice, when in contact with blood serum at room temperature for 30 minutes, was rendered almost completely inactive as regards its haematopoietic properties in rats. A haematopoietic principle was demonstrated with the same technique in the urine of normal person but not in urine of patients suffering from pernicious anaemia. Similar results were obtained when 9 patients with pernicious anaemia were given 10 to 15 daily enemata of 200 ml. of fresh urine of normal subjects. Clinically, a subjective improvement was observed in 5 patients, with a marked reticulocyte reaction in 3 and a weak reticulocyte reaction in 2 patients. A patient suffering from pernicious anaemia was treated in this way with the urine of another patient undergoing liver therapy for pernicious anaemia. There was a marked reticulocyte reaction in the second patient and after continuation of therapy haemoglobin value and erythrocyte count rose.

K. S. Zinnemann

2469. **The Loutit Type of Acquired Haemolytic Anaemia.** (Der Typus Loutit, eine neue Form von erworbener hämolytischer Anämie)
C. MAIER. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 983–984, Oct. 9. 1948.

In 1946 Loutit was able to demonstrate the presence of incomplete antibodies in some cases of acquired haemolytic anaemia. Among 34 cases of haemolytic anaemia, acquired and congenital, the author found one case of acquired haemolytic anaemia in which the presence of incomplete antibodies on the erythrocytes could be demonstrated with anti-human globulin serum. At the height of the disease antibodies were found in the serum too. These antibodies were not identical with rhesus agglutinins. The author proposes to separate these cases from the other cases of acquired haemolytic anaemias under the name of the Loutit type.

M. Schreuder (*Excerpta Medica*)

2470. **Hemolytic Anemia with Hemoglobinuria**
D. STATS, L. R. WASSERMAN, and N. ROSENTHAL. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **18**, 757–777, Oct., 1948. 2 figs., 7 refs.

The authors discuss their experience of haemolytic anaemias characterized by haemoglobinuria. Their cases fall into four categories: those of the Marchiafava–Micheli syndrome, those caused by cold agglutinins and by drugs (most frequently sulphanilamide), and an idiopathic variety. The various methods of investigation are considered, attention being directed to the value of spectroscopy of the blood and urine, and to the significance of haemosiderinuria, particularly in the Marchiafava–Micheli syndrome. Regarding treatment, the view is expressed that splenectomy is contraindicated in haemoglobinuria, and that vigorous blood transfusions constitute the measure of greatest value. In the Marchiafava–Micheli syndrome, however, no more transfusions should be given than are essential to control the anaemia, because of the frequency of post-transfusion reactions in this condition.

L. J. Davis

HAEMORRHAGIC DISEASES

2471. **The Value and the Limitations of the Coagulation Time in the Study of the Hemorrhagic Diseases**
A. J. QUICK, R. HONORATO, and M. STEFANINI. *Blood* [*Blood*] **3**, 1120–1129, Oct., 1948.

Procedures for determining the coagulation time of blood are based on the measurement of the interval between withdrawal of blood and the formation of sufficient fibrin to meet an arbitrarily designed end-point. Trustworthy results can be obtained only by performing the test under constant and rigidly controlled conditions in which the influence of all outside agents is excluded. Contamination of the specimen by traces of tissue juice containing thromboplastin should be avoided. Capillary blood is unstable, since it contains an uncontrollable amount of tissue fluid; it is therefore worthless for estimating coagulation time. In the United States the Lee and White test is gradually replacing other methods. This test is influenced by temperature, size of tube, and nature of tube surface. It should therefore be standardized at 37° C., and, since the size of the tube influences the speed of coagulation, a standard test-tube, which should be of glass and measure 13 × 100 mm., should be used. The authors recommend the following procedure for estimating coagulation time:

> After applying a tourniquet, blood should be drawn by venipuncture into a dry syringe. If blood is not obtained immediately without trauma another vein should be selected. One ml. is transferred to each of two scrupulously clean test-tubes and the tubes are placed immediately in a water bath at 37° C. The tubes are gently tilted every 30 seconds and the end-point taken as the moment when, on tilting, no flow of blood can be observed. The normal range is 5 to 10 minutes.

The authors stress the importance of bearing in mind that human blood clots within 12 seconds if it contains an optimum amount of thromboplastin. The curve correlating the coagulation time and the concentration of thromboplastin is a hyperbola with both asymptotes zero, and this explains why the coagulation time can be shortened from 1 hour to 5 minutes by an extremely small quantity of thromboplastin. The amount of thrombin formed depends on the quantity of prothrombin, thromboplastin, and calcium in the plasma and not on coagulation time.

Coagulation time may be prolonged in haemophilia, hypoprothrombinaemia, afibrinogenaemia, and heparinaemia. In haemophilia the coagulation time for an individual may remain constant for a relatively long time. Even when reduced to normal by plasma transfusion it always returns to this rather fixed value. Little thrombin is formed, as plasma lacks a thromboplastin precursor. Even if plasma contains enough thromboplastin to cause coagulation in normal time it may not supply enough thrombin for haemostasis. This explains why the clotting time is normal in known haemophiliacs. Such a finding may create a sense of false security in the surgeon; in addition, not every measure which reduces coagulation time in haemophiliacs is effective in controlling haemorrhage. Estimation of the clotting time is therefore of limited value in the diagnosis or treatment of haemophilia. A prolonged coagulation time is suggestive when other causes have been excluded, but a normal time does not exclude a diagnosis of haemophilia; a history of bleeding and a poor consumption of prothrombin during coagulation seem to be much more reliable evidence.

In hypoprothrombinaemia the coagulation time is affected to only a small extent; even with an extremely low prothrombin concentration it is rarely as prolonged as in a moderately severe haemophilia. At very low levels the prothrombin and the coagulation times tend to become identical. In afibrinogenaemia the blood is incoagulable, but a small amount of fibrinogen restores the clotting time to normal. As the presence of heparin in the blood increases the coagulation time, the authors suggest that the test can be used to control the therapeutic action of this drug. *R. Winston Evans*

2472. **The Relationship Between Heparin Dosage and Clotting Time**
L. B. JAQUES and A. G. RICKER. *Blood* [*Blood*] **3**, 1197–1212, Oct., 1948. 4 figs., 23 refs.

Addition of heparin to blood *in vitro* showed that the rise in heparin concentration had little effect at first, but that with bigger doses a small increase in concentration produced a great increase in the clotting time. When such results were compared with the response to variations in dose of heparin *in vivo* a measure of the individual's ability to remove heparin from the circulation was obtained. The sensitivity of the blood to heparin was found to depend on the individual; it also varied greatly with technique. Anaesthesia with ether caused an increase in sensitivity of the blood to heparin; urethane anaesthesia, the injection of indian ink, and evisceration caused a decrease. None of these procedures influenced the duration of heparin action.
Marjorie Le Vay

2473. **Anticoagulant Effect of Dicumarol at Various Prothrombin Levels in Dogs**
N. H. MOSS, R. L. SCHAFER, and C. K. KIRBY. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 143–145, Oct., 1948. 2 figs., 7 refs.

The authors studied the anticoagulant effect of dicoumarol at various prothrombin levels in dogs. Thrombosis was induced by insertion of a glass cannula into the femoral artery under anaesthesia with intravenous sodium pentobarbital. The system was filled with sterile physiological saline and connected to a mercury manometer. When thrombosis occurred the manometer ceased to oscillate. The prothrombin level was estimated by Quick's method with the plasma diluted 50% with normal physiological saline.

In 14 control animals the femoral artery was cannulated twenty-two times and thrombosis occurred in 3 to 10 minutes (average 6·3 minutes). The experimental series consisted of 32 dogs to whom dicoumarol was given in doses of 10 to 400 mg., usually 72 hours before the experimental procedure. Prothrombin levels of from

95 to 8% were obtained. The onset of thrombosis was not delayed at prothrombin levels above 40%; below 40% thrombosis occurred on the average in 16·6 seconds. In 10 of the dogs with prothrombin levels between 8 and 95% there was no correlation between the Lee-White coagulation time and the cannula " thrombosis " time. [This suggests that the cannula thrombosis cannot be strictly compared with clinical thrombosis and to that extent the value of these experiments as a guide to prothrombin treatment is lessened.] *A. W. H. Foxell*

2474. **Observation on the Mechanism of Action of Dicoumarol**
R. L. MACMILLAN. *Science* [*Science*] **108**, 416–417, Oct. 15, 1948. 5 refs.

Addition of normal plasma to dicoumarol plasma resulted in an increase in the prothrombin content of the mixture greater than could be explained by simple mixing of prothrombin solutions of different concentrations. Normal plasma may contain a prothrombin accelerator which is deficient in dicoumarol plasma. It is present also in normal serum, but removed by Seitz filtration. *A. Brown*

2475. **Effect of Rutin on Dicoumarolism**
W. G. CLARK. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 97–98, Oct., 1948. 16 refs.

There are conflicting reports on the effect of flavonoid derivatives (" vitamin-P "-like substances) on patients suffering from haemorrhagic symptoms following dicoumarol therapy. Three experiments are described in which rats were fed on mash containing varying doses of dicoumarol, with and without the addition of rutin. No significant differences were found in the survival rates of the control or rutin-fed group, nor were there any group differences in the onset or severity of haemorrhagic symptoms. *A. W. H. Foxell*

2476. **Presence of Mast Cells in Bone Marrow. I. Relations Between Mast Cells, Antithrombin, Platelet Formation, and Thrombokinase in Disease and in Experimental Studies.** (Sulla presenza di mastcellule nel midollo osseo. I. Rapporti tra mastcellule, antitrombina, piastrinopoiesii e trombochinasi nel malato ed in ricerche sperimentali)
P. MENEGHINI. *Minerva Medica* [*Minerva med., Torino*] **2**, 297–300, Oct. 6, 1948. 3 figs.

The mast cells in the bone marrow of patients with hepatic disease differ from those seen in other disorders of haematopoiesis. They have more vacuolations in the cytoplasm and are morphologically more like histiocytic elements. It is not certain why the coagulation time is prolonged in hepatic disease. In thrombocytopenic purpura it is prolonged because of lack of thrombokinase. Ferrata regarded mast cells as stroma elements of the marrow; other authors believe that they are normally present in the marrow. An increase in mast cells indicates greater production of heparin. Increased amounts of heparin are found in the blood in jaundice and in acute necrosis of the liver. In thrombocytopenic purpura hyperheparinaemia is only relative because thrombokinase is diminished.

The antagonism between heparin, which is produced by mast cells, and thrombokinase suggested that a study of the megakaryocytes in the marrow of patients with hepatic disease would give valuable information. In jaundice the more mature forms of megakaryocytes—for example, the platelet-forming ones—are more numerous than in the normal subject. Disease of the liver is characterized by increases in mast cells, in platelet formation, and in histiocytic reaction in the bone marrow. In guinea-pigs ligation of the common bile duct and injections of indian ink resulted in acceleration of the maturation of megakaryocytes, but injections of heparin did not produce abnormal figures of cells.

In a patient with carcinoma of the breast treated by *x*-irradiation, the maturation of megakaryocytes was inhibited. After injections of heparin the marrow showed marked improvement in the process of maturation, and the number of basophil cells was increased.

The presence of mast cells in the marrow has a definite pathological significance. *E. Neumark*

LEUKAEMIAS

2477. ***para*-Aminobenzoic Acid in Leukaemia. Effect on the Leucocyte-count**
H. B. MAY and J. VALLANCE-OWEN. *Lancet* [*Lancet*] **2**, 607–609, Oct. 16, 1948. 5 figs., 6 refs.

Five cases of chronic myeloid leukaemia, one of chronic lymphatic leukaemia, and one of acute leukaemia were treated with *para*-aminobenzoic acid, 0·5 g. per lb. (0·45 kg.) body weight per 24 hours. In the 5 cases of chronic myeloid leukaemia there was a pronounced fall in the total leucocyte count of the blood. When treatment was stopped the count returned rapidly to its former value. A second course of treatment resulted in a similar fall in the leucocyte count. The differential count of the leucocytes in the peripheral blood and the sternal marrow remained unchanged. The total leucocyte counts in the cases of chronic lymphatic leukaemia and acute myeloblastic leukaemia were unaltered. Toxic symptoms were noted from the treatment.
John F. Loutit

2478. **Atypical Effect of Urethane in Leukaemia.** (Atypische Urethanwirkung bei Leukämie)
S. GREIF. *Wiener Klinische Wochenschrift* [*Wien. klin. Wschr.*] **60**, 695–699, Oct. 29, 1948. 42 refs.

The mode of action of urethane in the leukaemias is reviewed, with special reference to 2 cases observed by the author. In the first case, one of typical chronic myeloid leukaemia, 5 g. of urethane was given by mouth for 18 days without any change in the blood or marrow picture, while the spleen, which reached the pelvis, remained the same size. A month after the patient was discharged from hospital the leucocyte count had fallen from about 50,000 per c.mm. to 9,000 per c.mm., a

general maturation being observed in the haemogram. This change is not regarded as being a spontaneous remission but as representing a delayed effect of the urethane, perhaps due to insufficient dosage [an unconvincing inference].

In the second case, also one of chronic myeloid leukaemia, leucocytes numbered about 20,000 per c.mm., with a fair percentage of premyelocytes and myeloblasts; the leukaemia was apparently in process of becoming acute. On two successive days 5 g. of urethane was given, and on the third day the leucocyte count had fallen to about 4,000 per c.mm. The drug was continued in the same dose for two more days, and the following day the leucocytes numbered 870 per c.mm., with 24% of myeloblasts and many premyelocytes and young myelocytes. It is inferred that urethane in this case accelerated the conversion of chronic leukaemia into acute leukaemia. Certainly the myelogram, which showed 12% of myeloblasts before the treatment was started, showed 72% of atypical ones at the end of treatment.

Apart from these findings the author's experience is the same as that of other workers—namely, that urethane is mainly of value in chronic leukaemia of the myeloid type. *A. Piney*

2479. **The Problem of Differentiation Potential of Leukaemic Cells.** (Zum Problem der Differenzierungspotenzen der Leukosezellen)
K. ROHR. *Schweizerische Medizinische Wochenschrift* [*Schewiz. med. Wschr.*] **78**, 991–993, Oct. 9, 1948. 5 figs., 8 refs.

Most investigators are of the opinion that the white cells observed in myeloid leukaemia originate from myeloblasts or haemocytoblasts. The present author believes, however, that these leukaemic cells originate from the myelocytes, promyelocytes, and promonocytes. If these cells become sufficiently differentiated in the process of maturation, the blood then shows mature but pathological leucocytes, " para-leucocytes ". Conversely, in other cases de-differentiation gives rise to " paramyeloblasts ", that is, the cells do not mature but assume a pathological aspect. This new conception explains the discrepancies between findings in bone marrow and in blood in certain cases of leukaemia in which the marrow contains essentially those cells which have given origin to the leukaemic elements of the blood, whereas the latter have changed their appearance, having had time to undergo differentiation or de-differentiation.
G. Hemmeler (*Excerpta Medica*)

RETICULO-ENDOTHELIAL SYSTEM

2480. **Boeck's Disease (Boeck's Sarcoid)**
J. ROSENTHAL and I. FEIGIN. *Archives of Pathology* [*Arch. Path.*] **45**, 681–693, June, 1948. 7 figs., 13 refs.

Four cases of Boeck's sarcoid coming to necropsy are described in detail. In one, a white woman who died of cerebral thrombosis, there was a small peripheral lung lesion and a little hyalinization in a paratracheal lymph node, and there must on the evidence be some uncertainty about the diagnosis; however, in the other 3 cases, all in negroes, the diagnosis was certain, one patient dying of subacute bacterial endocarditis, the second of pneumococcal meningitis, and the third of right heart failure due to pulmonary fibrosis consequent on diffuse lesions. In the first of these 3, repeated lymph node biopsy and one skin biopsy gave the diagnosis, in the second the diagnosis was made on clinical grounds alone, while in the last the diffuse lesions in the lungs were identified only after necropsy. All 3 showed a reversal of the normal plasma albumin–globulin ratio. In many of the lesions examined microscopically healing was observed at various stages. The authors describe and discuss in detail their observations on the progression of the essential lesion to the completely healed state, a feature of considerable interest and value in this paper; briefly, fibrosis and, particularly, hyalinization of the abundant eosinophil cellular cytoplasm are seen as end stages, giant cells being frequently the sole late survivors. Necrosis and calcification are not features. Complete regression of the smaller lesions seems possible.
W. S. Killpack

2481. **Studies on Nitrogen Mustards in the Treatment of Hodgkin's Disease and Related Conditions.** (Recherches sur des dérivés azotés de l'ypérite dans le traitement de la maladie de Hodgkin et d'affections voisines)
L. JUSTIN-BESANÇON, S. LAMMOTTE-BARILLON, C. POLONOVSKI, and —. BESTAUX. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **65**, 29–34, 1949. 2 refs.

In a previous communication (*ibid.*, 1948, **64**, 582) the synthesis in French laboratories of bromine and iodine derivatives of nitrogen mustard was announced. This paper reports the results of a clinical application of these derivatives in the light of the experience with the better known methyl bis (β-chloroethyl) amine. The bromine derivative, $CH_3N(CH_2CH_2Br)_2$, tried on 3 patients, appears to have exactly the same clinical effects as the chloride; the optimal dose is the same. Comparable results were obtained with the iodide, $CH_3N(CH_2CH_2I)_2$, in equimolecular doses. Thus in one patient a 28 mg. dose was insufficient and the clinical effect was slight. In a second patient, a female aged 50 with Hodgkin's disease for 2 years and pronounced anaemia due to *x*-ray therapy, 56 mg. in 4 days caused a general improvement, with fall in temperature, regression of cervical and mediastinal adenopathy, and considerable fall in leucocyte count, but this improvement lasted only for 8 days; subsequent treatment with the chloride was partly successful for a short time only. In 9 other cases doses of 62 to 85 mg. spread over 6 days produced uniformly favourable results. These cases were not followed up and the duration of the improvement was not ascertained. It emerges from this study that all three halogen derivates have a similar clinical action at equimolecular doses. The iodide has been used for 2 days longer than usual without inconvenience to the patients; its dose, 50% higher than the standard dose of the chloride, does not accelerate the fall in leucocyte count. *A. Lilker*

Respiratory Disorders

2482. **Pulmonary Alveolar Lining in Bronchiectasis**
C. F. WATTS and J. R. MCDONALD. *Archives of Pathology* [*Arch. Path.*] **45**, 742–751, June, 1948. 6 figs., 31 refs.

From each of 50 lungs removed surgically for bronchiectasis an average of three blocks was examined histologically—a small dilated bronchus, a portion of subpleural lung parenchyma, and, where possible, a uniformly atelectatic area. In the sections two relatively distinct types of alveolar cell lining were found: (*a*) square-cuboidal, or columnar, cells with dark-staining nuclei and acidophilic cytoplasm, non-phagocytic and packed in an uninterrupted layer; when found (17 cases) this type of epithelium was invariably in the peribronchial parenchyma, and in four instances continuity with bronchial epithelium was traceable (however, use was not made in this study of serial sections); (*b*) rounded-cuboidal, paler cells with vacuolated cytoplasm, often phagocytic and frequently scattered or in isolation. This second type of cell lining was found in subpleural parenchyma, in thickened interalveolar septa, and in the neighbourhood of scars, that is, distal to the terminal bronchi, in 43 of the cases. *W. S. Killpack*

2483. **The Segmental Distribution of Bronchiectasis**
H. E. COUNIHAN. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] **6**, 731–737, Nov., 1948. 4 figs., 9 refs.

The distribution of the bronchial disease in 149 cases of bronchiectasis is analysed. The results differ little from those of previous investigations. The dorsal-lobe bronchus was normal in about half the cases of lower-lobe bronchiectasis. *J. R. Bignall*

2484. **Problems in Determining the Bacterial Flora of the Pharynx**
COMMISSION ON ACUTE RESPIRATORY DISEASES. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 45–52, Oct., 1948. 2 figs., 23 refs.

The various species obtained by culture of pharyngeal swabs are more accurately represented when plating is carried out from a well-mixed suspension prepared by washing the swab in broth than when plates are directly inoculated with the dry swab.

In a comparative test, 1 or more of 4 species present was detected by using a broth suspension in 22 instances when the dry swab failed to reveal the flora, while the reverse was true only in 4 cases. Mixing an inoculum in 3 ml. 20 times with a 5 ml. pipette produced a homogeneous suspension of haemolytic streptococci, and an almost homogeneous one of *Staphylococcus pyogenes*, *Haemophilus influenzae*, and a Gram-negative coccus. Nevertheless the normal sampling variation is such that more accurate results are obtained when several plates are inoculated from the broth suspension. Colony selection and identification are improved by the use of a wide-field binocular microscope; this was particularly obvious in the case of pneumococci.

The relative distribution on multiple fields of plates of 2 species of bacteria from a mixed broth suspension shows less variation than would random distribution, and indicates some relation between the growth of the two species. This was more marked with a mixture of *H. influenzae* and streptococci than with a mixture of streptococci and staphylococci, but was still observed with the latter. Conditions of symbiosis and antibiosis will affect relative and absolute bacterial growth from mixed inocula such as are obtained from the pharynx, hence plating does not necessarily reflect either pharyngeal occurrence or distribution of the organisms in such inocula.

The use of Pike's [fluid enrichment in sodium azide, crystal violet broth] method was found to be of value for streptococci, the carrier rate being increased from 9·6 (as otherwise determined) to 20·8 by its use. The effect was greatest, however, on group B streptococci and least on "typeable" strains of group A. *G. T. L. Archer*

2485. **Hereditary Hemorrhagic Telangiectases associated with Pulmonary Arteriovenous Fistula in Two Members of a Family**
J. H. MOYER and A. J. ACKERMAN. *Annals of Internal Medicine* [*Ann. intern. Med.*] **29**, 775–802, Nov., 1948. 15 figs., 57 refs.

This is an account of 2 cases of hereditary haemorrhagic telangiectasis in brothers with the special manifestation of pulmonary arterio-venous fistula. The patients suffered from breathlessness, weakness, palpitation, and haemoptysis, with cyanosis and polycythaemia. Clubbing of the fingers and toes was seen in one of the patients together with the symptoms of anoxaemia. There is a full discussion of the pathology of the condition. [This section is illustrated with excellent radiographs.]
G. F. Walker

2486. **Arterio-venous Anastomoses in the Pulmonary Circulation.** (Об артериовенозных анастомозах малого кругакровообращения)
A. V. RIVKIND. Архив Патологии [*Arkh. Patol.*] **10**, No. 6, 42–53, Nov.–Dec., 1948. 5 figs., 30 refs.

A system of intervascular channels can be demonstrated around the smaller bronchioles in the lung. Its chief link is an occluding arteriole, a branch or segment of the bronchial artery. This occluding arteriole contains longitudinal muscle bundles in its intima together with a network of elastic fibres which may be con-

tiguous with the internal elastic lamina. These anatomical features are somewhat variable, and the elastic fibres in particular may be completely absent. The occluding arteriole can contract either at its point of origin or at other points along its course. A series of arterio-venous anastomoses connects it with the venous plexus surrounding the bronchiole and through it with the pulmonary vein; it is also linked by another series of interarterial connexions with the corresponding pulmonary artery. This system of communications is absent at birth but is found with increasing frequency in later life, more especially in pathological conditions associated with pulmonary hypertension.

Circulation is as follows. If the occluding artery closes at its point of origin, blood will flow from the pulmonary artery through the interarterial channels, the occluding arteriole, and the bronchial venous plexus into the pulmonary vein. The pulmonary vein will thereby acquire a raised content of non-oxygenated blood. If the interarterial channels are closed, diverted blood will flow from the bronchial artery through the occluding arteriole and the venous plexus into the pulmonary vein which will now contain a higher proportion of oxygenated blood. Lastly, if the arterio-venous anastomoses proper are closed, some blood will be diverted from the bronchial into the pulmonary artery and more oxygenated blood will reach the lung alveoli. The diverting force will in each case be the difference in the head of pressure playing upon the variously constricted or patent vascular channels. It will also be noted that blood shunted from the high-pressure bronchial artery into the low-pressure pulmonary venous circulation will tend to boost the pressure of blood returning to the heart.

The above description is only a schematic representation. In reality there must be a much more complex mechanism. Blood is shunted through the arterio-venous channels, like the stream of air split by the stops of a clarinet. While the existence of these channels has been adequately demonstrated, their function and rhythm remain a matter for inference and speculation. Under physiological conditions they may perhaps have three functions: (1) To help in the regulation of the respiratory exchange of gases. (2) To regulate the amount of residual blood in the lungs—the pulmonary blood depot. When blood is diverted from the arterial systems into the veins, walls of the bronchioles swell with the engorgement of their venous plexus. Air entry into alveoli is restricted, and there is at the same time a relative stasis in the distal part of the arterial circulation. The result is a condition which may be described as physiological atelectasis. (3) To play an important part in the maintenance and regulation of the pulmonary blood pressure.

These anatomical facts also shed new light on the mechanism of some pathological conditions. Bronchitis accompanying essential emphysema is "inevitable" because it is caused by the active engorgement, and not passive congestion or inflammatory hyperaemia of the bronchial venous plexus. Cyanosis which is sometimes present in various conditions without cardiac or respiratory failure can be explained by the shunt from the pulmonary artery into the pulmonary vein. The presence of large calibre anastomoses (60 μ and more) also explains paradoxical embolism in cases where the foramen ovale is closed, as well as some hitherto unaccountable metastases of tumours. It will be appreciated, on the other hand, that arteriosclerotic changes, when they occur, will inevitably disrupt the delicately adjusted distributing process and lead, among other things, to a hypertrophy of the right side of the heart.

L. Crome

2487. **Studies in the Oral Administration of Penicillin. III. Oral Penicillin in the Treatment of Pneumococcic Pneumonia**

I. F. VOLINI, W. HOFFMAN, J. R. HUGHES, and J. R. PEFFER. *Illinois Medical Journal* [*Illinois med. J.*] **94**, 235–242, Oct., 1948. 7 figs., 11 refs.

This is a study of 48 unselected cases of pneumococcal pneumonia treated with penicillin by mouth. The drug used was pure crystalline potassium penicillin assaying slightly over 1,500 units per mg. and containing over 95% of penicillin G. It was given in the form of tablets made up with hydrogenated fat, salts of fatty acids, and starch, was administered without regard to the time of meals, and was not buffered in any way. The patients were given 200,000 units as a loading dose and 100,000 units 3-hourly thereafter. The average duration of treatment was 5·8 days. On this regimen therapeutic blood-levels of penicillin were obtained and the clinical results were satisfactory. Three patients died and 5 failed to respond satisfactorily to the drug, but the rest responded as rapidly as they probably would have done to parenteral penicillin. Only one very mild penicillin reaction (skin erythema) was noted. In 25 cases the pneumococci were typed, and the results indicate that the average virulence of the organisms in these cases was slightly greater than the average of similar reported series.

[This paper is not well presented; it is not clear, for example, whether 21 "untyped" cases were in fact of pneumococcal origin. There were 2 deaths among the 26 proved cases. As the authors admit, the disadvantage of oral penicillin in pneumonia is the cost of treatment, which is five times that of sulphonamide therapy.]

John R. Forbes

2488. **Apical Pulmonary Carcinoma and Tuberculosis. The Value of Sputum Cell Study in the Differential Diagnosis**

M. BERGMANN, B. A. SHATZ, and I. J. FLANCE. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 798–801, Nov. 13, 1948. 6 figs., 14 refs.

The authors describe 3 cases of bronchial carcinoma involving the upper lobe in which a mistaken diagnosis of pulmonary tuberculosis was corrected by the demonstration of carcinoma cells in the sputum. The dangers of mistaking apical carcinoma for pulmonary tuberculosis are emphasized and the value of examination of the sputum for malignant cells in cases in which bronchoscopic biopsy is not possible. *J. W. Litchfield*

Digestive Disorders

STOMACH

2489. **The Effects of Some Synthetic Antispasmodic Agents on Human Gastric and Duodenal Functions**
J. R. HIGGINS, A. M. SCHOEN, and P. K. KNOEFEL. *Gastroenterology* [*Gastroenterology*] **11**, 508–518, Oct., 1948. 2 figs., 12 refs.

Clinical trials with three synthetic antispasmodics were made on patients with duodenal ulcers. The drugs were the diethylaminoethyl esters of fluorene-9-carboxylic acid, of 9-10-dihydroanthracene-10-carboxylic acid, and of xanthene-9-carboxylic acid. On many occasions patients reported that after taking these agents their pain disappeared in 10 to 15 minutes and did not return for several hours.

Laboratory trials were made on 10 patients. Gastric motility was measured directly by a manometric method, while the use of a double-lumen tube enabled a simultaneous determination of secretory rate, the *p*H, the peptic power, and the emptying rate of the gastric secretion. The relief of pain was attributed to the reduction of motility, " as there was no fall in acidity ". [The evidence for this statement is obscure, since the *p*H does not appear to have been measured in the duodenal cap.] The route by which the drugs were given is important. Atropine intravenously was more effective in reducing motility than either intragastrically or intraduodenally. With the synthetic drugs the intraduodenal route was the most and the intravenous route the least effective. With atropine the reactions were pronounced, and the route made no difference. With the synthetic drugs there was no trouble with reactions except when the intravenous route was used. The authors conclude that the site of action is " possibly on the duodenal mucosa, and the response may be mediated by a duodeno-gastric reflex ".

[The results are tabulated in such a way that statistical criticism is impossible. There is no record of control injections of water or other substances having been used, and it would seem possible that the results might be due to non-specific irritation of the duodenum exciting the normal duodeno-gastric inhibitory reflex].

Denys Jennings

2490. **Lysozyme Activity in Ulcerative Alimentary Disease. I. Lysozyme in Peptic Ulcer**
K. MEYER, J. F. PRUDDEN, W. L. LEHMAN, and A. STEINBERG. *American Journal of Medicine* [*Amer. J. Med.*] **5**, 482–495, Oct., 1948. 10 figs., 9 refs.

Lysozyme is a bacteriolytic agent which is present in many secretions. Lysis of susceptible organisms is due to hydrolysis of a mucoid component of the cell wall. Lysozyme can be estimated quantitatively, and a unit is defined as the amount which in ten minutes, under standard conditions, reduces to one-half the viscosity of a standard substrate.

Extraction of pieces of gastric and duodenal mucosa, taken from animals and from human resection specimens, demonstrated a rich lysozyme content in the pre-pyloric and post-pyloric regions. Test meals in 30 normal subjects, 29 patients with ulcers not operated on, and small groups of patients with gastro-intestinal disorders showed a raised lysozyme content in the gastric juice of patients with ulcer. [This part of the research is badly controlled and it is impossible to assess its significance.] Finally, lysozyme was fed to dogs in various ways in concentrations of the order of 7,500 units per ml. Lysozyme dripped into a gastric pouch of an anaesthetized dog for 4 hours resulted in removal of the protective mucous coat of the epithelium, in histological changes, and in the formation of a small area of superficial erosion. Lysozyme given to 3 dogs for periods up to 38 days caused loose stools in every case. Necropsy revealed loss of the gastric mucus but no other lesion in the stomach. The small intestine and colon, on the other hand, were hyperaemic, oedematous, and in places ulcerated.

The authors claim to have demonstrated that lysozyme is possibly of significance in the production of human peptic ulcer. The most important single factor protecting the epithelium from self-digestion is the mucous coat, and this might be destroyed locally by an increased output of lysozyme.

Denys Jennings

2491. **Vagotomy and the Hunger-producing Action of Insulin in Man**
M. I. GROSSMAN and I. F. STEIN. *Journal of Applied Physiology* [*J. appl. Physiol.*] **1**, 263–269, Oct., 1948. 11 refs.

Carlson, following Cannon and Washburne, associated true hunger pangs with synchronous gastric contractions. Weakness, headache, and nausea were regarded by him as accessory hunger phenomena which might overshadow the pressure-pain sensation from the stomach. He also stated that the " vagi nerves are the main, if not the only, afferent pathway for the gastric hunger impulses ". This paper deals with the effects of insulin on gastric motility, secretion, and hunger before and after bilateral vagotomy in man. It is generally held that the hypoglycaemia induced by insulin stimulates the vagal centres, causing an increase in gastric motility. In the intact man gastric secretion started before hunger was reported. After vagotomy, subsequent to the intravenous injection of 15 units of insulin, hunger was reported after the maximum hypoglycaemia had passed; it never began before 30 minutes after the injection, and usually lasted until food was given. Of the 18 subjects examined before vagotomy 12 experienced hunger after insulin; after vagotomy 20 out of 23 subjects had hunger

pangs. Four subjects who did not experience hunger when given insulin before operation did so after the operation. The hunger sensation was not confined to the epigastrium but was described as a diffuse abdominal emptiness and weakness associated with a desire for food. Motility tests were made on 15 subjects before operation: spontaneous gastric contractions were observed both before and after the insulin injection, but in only 4 subjects did typical gastric distress synchronize with gastric contractions. Gastric motility and secretion were not provoked by insulin in all 23 subjects after vagotomy, nor was the character of the hunger sensation produced by insulin unaltered after the operation.

Two subjects were examined before and after a bilateral sympathectomy for hypertension. Before the operation each " hunger " contraction was recognized as a sensation of epigastric distress; post-operatively gastic contractions occurred with about the same vigour and frequency but they no longer caused distress. *C. C. N. Vass*

2492. **Replacement Therapy in Gastrointestinal Hemorrhage**

V. GINSBERG, I. HIRSCHLEIFER, N. RITZ, and I. R. SCHWARTZ. *Review of Gastroenterology* [*Rev. Gastroent.*] **15**, 747–757, Oct., 1948. 2 figs., 27 refs.

As there is still a controversy about the place of blood transfusion in the treatment of acute gastro-intestinal haemorrhage the authors analysed a series of 32 cases. All patients received 1,000 ml. of whole blood daily till a haemoglobin value of 13 g. per 100 ml. was reached. Age was not regarded as a contraindication: 3 of the patients were 70 or over. There was a slight rise in the blood pressure after the first transfusion. No deaths occurred from overloading of the circulation, continued bleeding, or blowing out of the clot. Raised blood-urea levels fell quickly with this treatment. The persistence of raised values is evidence of continued or fresh bleeding. The only contraindications are cardiac disease, hypertension, and nephritis. The rate of transfusion advised is 1½ to 2 hours for 1,000 ml.

R. Schneider

2493. **Failure of an Extract of Pregnant Mares' Urine to Influence Gastric Secretion in Man**

J. B. KIRSNER, E. LEVIN, and W. L. PALMER. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 108–111, Oct., 1948. 2 figs., 15 refs.

An extract of pregnant mares' urine, " kutrol ", having no gonadotrophic activity, has previously been shown to afford some protection against ulcer formation in the Shay rat, and to have some beneficial effect when given repeatedly in a total daily dose of 0·6 g., in cases of chronic duodenal ulcer in human beings. The present report, from the University of Chicago Department of Medicine, shows that there is no decrease in the production of gastric juice or of hydrochloric acid when even 7·5 g. of kutrol is given by stomach tube to patients suffering from peptic ulcer. Tests were made on both fasting and nocturnal secretion in 12 patients.

[It would be interesting to know, but less easy to determine, whether continued treatment of these patients with the same batch of extract by mouth had any specific effect on the ulcers in the absence of secretory inhibition.]

Derek R. Wood

INTESTINES

2494. **The Maintenance of Patients with Tropical Sprue by Means of Massive Doses of Synthetic 5-Methyl Uracil (Thymine)**

G. G. LOPEZ, F. MILANES, R. LOPEZ TOCA, T. ARAMBURU, and T. D. SPIES. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 270–274, Sept., 1948. 4 figs., 6 refs.

The authors have previously demonstrated that large doses of thymine produce clinical and haematological improvement in the macrocytic anaemias of pernicious anaemia, of nutritional deficiency, and of tropical sprue. Thymine is several thousand times less active than folic acid.

In the present paper are reported 3 cases of tropical sprue maintained in remission for at least a year by thymine. Diet in hospital contained no meat, fish, poultry, milk, or eggs. The dosage of thymine was 7·5 g. twice a day. Reticulocytosis started on the 4th or 5th day and reached a peak on the 8th or 9th day. By the 10th day there was almost complete megaloblastic arrest, as indicated by marrow puncture. Clinical improvement started at the same time: appetite increased, glossitis disappeared, and the patients gained weight; their stools improved, becoming normal in 6 weeks. The 3 patients were respectively 160, 159, and 112 days under observation in hospital, and were followed up for a further year after leaving hospital and ceasing thymine therapy.

Thymine is not recommended as a practical therapeutic agent. It has no known advantages over the much more active folic acid. *C. L. Cope*

2495. **Folic Acid in Non-tropical Sprue: with Particular Reference to Fat Absorption and Radiological Appearances of the Small Intestines**

J. W. FERGUSON and F. CALDER. *Glasgow Medical Journal* [*Glasg. med. J.*] **29**, 341–356, Oct., 1948. 13 figs., 18 refs.

This is a report on the effect of folic acid in 7 cases of non-tropical sprue. The patients were observed for 2 weeks before treatment was started, and then 20 mg. folic acid was given daily for 14 days. Fat balance, blood count, biochemical changes, and radiological appearances were studied before and after treatment. Only in those cases in which there was a megaloblastic bone-marrow reaction was there any significant response to folic acid. In these cases not only did the blood picture revert towards the normal, but there was an improvement in the general condition, the diarrhoea became less, and the patient gained in weight even though no significant change was discernible in the fat content of the stool. The so-called deficiency pattern of sprue

changed to normal in 2 cases in which there was megaloblastic marrow reaction of comparatively short duration, in spite of there being no improvement in the steatorrhoea; in one of these there was no clinical or haematological improvement. *A. H. Douthwaite*

2496. **Nonspecific Enterocolitis**
E. S. OLSAN and M. L. SUSSMAN. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **60**, 471–485, Oct., 1948. 6 figs., 23 refs.

In 5 to 10% of patients with ulcerative colitis the disease is limited to the right side of the colon. Sometimes the terminal ileum is also involved, and at laparotomy there is a close resemblance to regional ileitis. Few careful necropsy records have been published of this intermediate group of cases and the 9 long case reports in this paper are an attempt to fill the gap. In 2 of these cases ulcerative colitis was diagnosed during life, but necropsy revealed a normal colon and Crohn's disease of the small intestine. In 5 cases the clinical course was that of ulcerative colitis involving the whole colon, but necropsy revealed in addition a severe recent acute ulcerative process involving the ileum and jejunum. In another case the clinical course was that of regional jejuno-ileitis and this diagnosis was confirmed at laparotomy 4 years before death. Necropsy, however, showed ulcerative colitis and acute recent ulceration of the small intestine, but no evidence of a long-standing chronic process in the small intestine. Either the original findings at laparotomy must have been due to local areas of oedema in the small intestine, or if there had been a granulomatous condition it must have resolved completely. The last case was that of a man who developed ulcerative colitis at the age of 20, and after a series of relapses (mainly in the winter months in association with upper respiratory infections) died at the age of 29 with generalized amyloidosis. Necropsy revealed "relatively dormant" ulcerative colitis and "hyperacute" jejuno-ileitis with a recent perforated jejunal ulcer as the immediate cause of death. No explanation for the severe small intestinal ulceration could be found. The early ulcers, which were specially examined, showed no evidence of amyloidosis and the cytology of the lesions was not characteristic of any of the known granulomata.

[For fuller details the original paper must be read. There are good references to the literature.]

Denys Jennings

2497. **Lysozyme Activity in Ulcerative Alimentary Disease. II. Lysozyme Activity in Chronic Ulcerative Colitis**
K. MEYER, A. GELLHORN, J. F. PRUDDEN, A. L. LEHMAN, and A. STEINBERG. *American Journal of Medicine* [*Amer. J. Med.*] **5**, 496–502, Oct., 1948. 3 figs., 3 refs.

Previous work (see Abstract 2490) suggested that lysozyme might be important in the aetiology of ulcerative colitis. The authors therefore estimated the lysozyme content of normal stools (6 cases), of stools obtained by purging with castor oil and magnesium sulphate (8 cases), and of stools in idiopathic diarrhoea (3 cases) and in ulcerative colitis (32 cases). The stools in ulcerative colitis contain about 30 times as much lysozyme per gramme of wet weight as any other group; and the total output in 24 hours is about 170 times the output in normal stools, and about 26 times that in stools obtained by purging. Purging, although it increases the yield over 24 hours, decreases the output per gramme of wet weight.

Further observations showed that this huge increase in lysozyme production in ulcerative colitis was due to the colon. The amount of lysozyme in the ileal contents of 3 patients after ileostomy was normal; the amount in the colonic mucus of patients with idiopathic diarrhoea and colonic carcinoma was also normal. But surface mucus from the rectosigmoid of patients with ulcerative colitis was very rich in lysozyme, and in 9 patients improvement or exacerbation of the clinical state was accompanied by corresponding changes in the stool lysozyme. Attempts to apply these results by giving therapeutic enemata of lysozyme inhibitors failed, the failure being ascribed to the production of protein in the colon which binds the inhibitors and prevents their action.

[The authors' conclusion that lysozyme is an "etiologic factor in ulcerative colitis" may or may not be true, but it is unjustified on the evidence they publish.]

Denys Jennings

LIVER; PANCREAS

2498. **Combined Liver Biopsy and Liver Function Study in 132 Cases of Cholelithiasis and 31 Cases of Peptic Ulcer (Operated Cases). (Emphasis upon Early Microscopic Liver Disease and Particularly Acute Infiltrative Hepatitis and Microscopic Periportal Cirrhosis)**
J. G. MATEER, F. W. HARTMAN, J. I. BALTZ, L. D. FALLIS, A. B. MCGRAW, and H. H. STEELE. *Gastroenterology* [*Gastroenterology*] **11**, 284–302, Sept., 1948. 4 figs., 10 refs.

Wedge biopsy specimens were taken from the edge of the liver in 163 patients who had undergone laparotomy, 31 of them for peptic ulcer and the rest for cholelithiasis. Only a very small percentage of each group had what the authors considered to be histologically normal livers. In a high proportion the chief finding was an increase of periportal connective tissue, but a smaller proportion showed a condition characterized by polymorphonuclear infiltration of the parenchyma without necrosis, which is named by the authors "acute infiltrative hepatitis". Most of the patients in whom these conditions were found had had multiple attacks of gall-stone colic, but similar changes also occurred in 3 patients with peptic ulcer. Needle biopsy was made in 55 patients who had also been subjected to "wedge" biopsy. Although the histological findings by both methods are comparable, the former tended to show more fibrous stromal tissue. Various liver-function tests were carried out on 132 of the 163 patients subjected to liver biopsy. On the whole there was little correlation between abnormal pathological findings and abnormal results of liver-function tests, although a correlation was found between abnormal parenchymal changes and abnormal reactions to the

cephalin–cholesterol flocculation, bromsulphalein excretion, and urinary urobilin excretion tests and abnormal serum albumin values. However, numbers of patients without parenchymal changes gave abnormal test results, and it is concluded that " information regarding liver function and liver structure must be considered as more or less separate items of diagnostic value ".

[The authors assume that the so-called liver-function tests are in reality direct tests of liver function, but as the mechanism of many such tests is unknown, and the normal range of values in most of them is wide, this assumption appears to be unjustified. Those interested in liver pathology should see the original paper for descriptions and photomicrographs of " acute infiltrative hepatitis ".] *John Naish*

2499. **The Inactivation of Estrogens by Lipotropic Substances. Studies of Liver Dysfunction. II**
S. WALDMAN and L. PELNER. *Review of Gastroenterology* [*Rev. Gastroent.*] **15**, 762–765, Oct., 1948. 13 refs.

On the strength of the knowledge that the normal liver inactivates oestrogens and that signs of oestrogen overabundance are not uncommon in liver disease, the authors treated cases of menorrhagia and of loss of libido with methionine and choline. The menorrhagia (2 cases) was due to cystic ovaries. All 5 cases of loss of libido occurred in men—2 diabetic patients, and 3 otherwise normal individuals. In no case was there any obvious evidence of liver disease. Liver function tests did not show any abnormality [the test used is not stated]. All cases responded to treatment with either substance. In the diabetic patients choline not only led to return of libido but also to improvement in the diabetes itself. *R. Schneider*

2500. **Effect of Thiouracil on Liver Regeneration**
M. J. FOGELMAN and A. C. IVY. *American Journal of Physiology* [*Amer. J. Physiol.*] **153**, 397–401, June, 1948. 19 refs.

On the basis of observations by Paschkis *et al.* that thiouracil inhibits or prevents formation of hepatic tumours induced by 2-acetaminofluorene or *p*-dimethylaminoazobenzene it was originally thought that this might be due to inhibition of the rate of liver regeneration by thiouracil. Experiments reported here show the reverse to be true; thiouracil, when administered to partially hepatectomized rats, increases the rate of regeneration of the liver. This is in line with other experimental work indicating that thiouracil ameliorates certain liver diseases.

Although thiouracil depresses thyroid function and lowers metabolism, it is not certain that this is responsible for its action on the regenerating liver. The fact that it increases total liver weight, total liver protein, and the rate of regeneration of the liver—phenomena which most probably do not occur in association with a hypothyroid state produced by thyroidectomy—suggests a direct effect. The finding that prolonged feeding of thiourea tends to produce benign hepatomata with minimal cirrhosis points to a direct stimulating effect of thiouracil on the growth of the liver. *H. Pollak*

2501. **Hepatic Coma. Clinical and Laboratory Observations on Forty Patients**
T. L. MURPHY, T. C. CHALMERS, R. D. ECKHARDT, and C. S. DAVIDSON. *New England Journal of Medicine* [*New Engl. J. Med.*] **239**, 605–612, Oct. 21, 1948. Bibliography.

This paper deals with the fatal coma in 40 patients with chronic hepatic disease in whom liver function finally failed. Cirrhosis was the common disease, and there was often a history of alcoholism. The authors discard the old term cholaemia, dating from Leyden (1866), which is analogous to the term uraemia. Both terms were, of course, erroneous in their chemical conception, but are still found convenient by many.

The authors divide their cases into two groups: uncomplicated hepatic coma, where hepatic failure was apparently the sole cause of coma, and complicated hepatic coma, in which lobar pneumonia, cardiac failure, or tuberculosis, was also present. The first group is the interesting one, and the clinical aspects of the coma are well described. Lethargy sets in, followed by a stage of noisy confusion and finally deep coma. Death in this group occurred from 12 hours to 6 days after coma supervened; more than half of the patients died within 48 hours. The authors note again the evil effect of hypnotics and sedatives, especially morphine, which may precipitate the final coma.

Many laboratory investigations were carried out. In no case was the blood-sugar level (Folin–Wu method) dangerously low, the minimum figure being 68 mg. per 100 ml. Only in one patient did the coma respond to glucose intravenously, and then the response was temporary. The authors contrast this with the dramatic effect of sugar in dogs subjected to hepatectomy; but a patient who has had prolonged and gradual failure of liver function cannot be compared with a previously healthy dog. None of the laboratory findings threw any light on the chemical nature of the metabolic disorder associated with hepatic coma. Active feeding, by stomach tube or parenterally, with sugar, liver extracts, protein hydrolysates, and vitamins, was entirely without effect.

[This is a good account of the terminal coma of chronic hepatic failure, but readers should note that the coma of acute failure (acute hepatic necrosis) has differences.] *J. W. McNee*

2502. **The Relationship of Fibrocystic Disease of the Pancreas to a Deficiency of Secretin**
A. H. BAGGENSTOSS, M. H. POWER, and J. H. GRINDLAY. *Pediatrics* [*Pediatrics*] **2**, 435–442, Oct., 1948. 27 refs.

The authors present arguments in support of the hypothesis that fibrocystic disease of the pancreas is due to a congenital deficiency of secretin.

Pancreatic lesions similar to those of fibrocystic disease may occur in adults suffering from diseases which produce vomiting, gastric distension, mental discomfort, and dehydration. Inhibition of the type of pancreatic secretion normally stimulated by secretin is held to be responsible for these lesions. Secretin produces a flow

of alkaline fluid which dilutes the thick viscid juice produced by nervous stimulation of the pancreas and by pancreozymin. The hypothesis of secretin deficiency accords with the facts that fibrocystic disease is present at birth, is not a true malformation but manifests itself late in pregnancy, and is progressive. Chronic malnutrition resulting from loss of pancreatic function aggravates the condition. The other clinical and pathological manifestations of the disease such as congenital intestinal obstruction, lesions of the liver and biliary passages, and respiratory tract infection are also explained by the hypothesis. In congenital intestinal obstruction, inspissated meconium resulting from failure of pancreatic digestion is the main factor. Intrahepatic biliary obstruction may also be due to lack of secretin and account for the hepatic lesions. The pulmonary lesions are attributed to nutritional disturbances, including vitamin A deficiency, resulting from lack of pancreatic function.

Other theories are discussed. There is no evidence that a primary deficiency of vitamin A is responsible; congenital stenosis or atresia of the pancreatic ducts is found in a few cases only. There is no evidence that abnormal parasympathetic stimulation is responsible for the disease.

It was found possible to extract secretin from the upper part of the intestinal tract of persons 2 months to 73 years old. In the newborn it was necessary to concentrate the crude extracts from a number of specimens in order to obtain a sufficiently concentrated extract to produce a response in a dog with a total pancreatic fistula. Secretin can be successfully extracted up to 15 hours post mortem. If the specimen is kept in a frozen state, extraction can be delayed without loss of activity for as long as 39 days. In one case of fibrocystic disease of the pancreas studied by this method the authors found no evidence of secretin in the duodenum and upper part of the jejunum. *P. T. Bray*

See also Section Pathology, Abstract 2348.

PERITONEUM

2503. **Diagnosis and Pathogenesis of Fat-Containing Effusions in Body Cavities. A Case of Chylous Ascites and Chylothorax; Isotope Technique in Differential Diagnosis.** (Zur Diagnose und Pathogenese fetthaltiger Ergüsse der Körperhohlen: mit Mitteilung eines Falles von Chylaszites und Chylothorax, Isotopen-Technik zur Differentialdiagnose)

W. Bubb. *Gastroenterologia* [*Gastroenterologia, Basel*] 74, 42–64, 1948. 14 figs., 37 refs.

A single case, investigated and reported in detail, provides an excuse for a critical review of the literature and the presentation of a new hypothesis. A waiter aged 46 was admitted to Zürich University medical clinic and died 6 months later. The previous history was negative except for a history of abdominal swelling in childhood. He was healthy until a month before admission to hospital, when coughing, breathlessness on exertion, and sweating with a normal temperature caused him to consult his doctor, who made a presumptive diagnosis of polyserositis. Clinically there was massive ascites with a large right pleural effusion. Apart from clubbing of the fingers the other systems were normal. He was afebrile and the erythrocyte sedimentation rate was not increased. Pathological investigations revealed a normal blood picture and substantially normal blood chemistry, except for lowered total plasma protein concentration (5·1 g. per 100 ml.) and a big increase in the plasma fatty acid content (905 mg.) per 100 ml. Repeated tappings led to the removal of 65 litres from the right pleura and 59 litres from the peritoneum. The fluid was always sterile, and even in that obtained at the first tappings there were many fat-containing endothelial cells, polymorphonuclear leucocytes, lymphocytes, and occasional red cells. The specific gravity was about 1015, protein 3 to 4 g. per 100 ml., fatty acids 1,900 mg. per 100 ml.; large clumps formed which stained irregularly with Sudan III. There was a slight diminution in serum albumin and an increase in α and β globulins (the chief lipid carriers) at the expense of γ globulin. Postmortem examination showed an old partially recanalized thrombosis of the innominate vein which was thought to be secondary, dilatation and thickening of the thoracic duct, and chronic inflammation of the mesentery and visceral peritoneum. Many fat-containing phagocytes were present in the mesentery and in the enlarged para-aortic, mesenteric, and inguinal lymph nodes.

Fatty exudates can be divided into true chylous ones due to trauma or obstruction, chyliform exudates where the fat is due to destruction of cells, and a mixed group where both these processes occur. The true chylous exudates are distinguished by the fine size of the fat particles, the relatively high fat and protein content, and the paucity of the cells. The exudate in the case reported could not be classified, and the final proof that chyle was responsible was elicited only by feeding a fat containing deuterium. The " marked " fat could be recognized in the exudate within a few hours of giving it by mouth.

The three possible causes of fatty exudates are: tears in the large ducts, multiple ruptures of smaller ducts due to obstruction, and damage to the walls of the system leading to an increase in permeability. The importance of the first two causes is overestimated in the literature. Trauma accounts for less than 10% of all reported cases, and the fistula is almost invariably in the thorax. Obstruction due to carcinomatous metastases is present in about a third of cases, and tuberculosis, usually in the region of the thoracic inlet, is also common. Numerous animal experiments, however, show the readiness with which collaterals form anastomoses with the veins, and permeability changes are probably really responsible in most cases. In some of the carcinomatous and tuberculous cases toxins may be the cause. In a large number of cases where non-specific peritonitis is present the possibility of a disturbance of fat metabolism should be considered. Animal experiments demonstrated that, if failure of resynthesis of fatty acids into fat should occur, it would provide an explanation of the histological findings in cases resembling the one reported: it would also explain the small group of cases classified as of intestinal fat dystrophy or Whipple's disease. *Denys Jennings*

Endocrine Disorders

2504. **Frontal Hyperostosis (Morgagni's Syndrome).** (Zgrubienie kości czołowej. (Hyperostosis frontalis, Zespól Morgagni'ego))
W. HARTWIG. *Polski Tygodnik Lekarski* [*Polsk. Tyg. lek.*] 3, 1233–1237 and 1265–1271, Oct. 18 and 25, 1948. 3 figs., 46 refs.

The thickening of the frontal bone with characteristic hyperostosis of its internal lamina is generally regarded as uncommon. It may occur together with obesity, hirsutism, and other endocrine or neuropsychiatric disorders. This clinical syndrome has often been referred to as Morel–Stewart's syndrome, but the author suggests that it was Morgagni who in 1761 first described the typical hyperostosis of the frontal bone. In this paper a survey of the literature of this condition is given and 4 new cases are described. The syndrome, which occurs almost exclusively in women approaching the climacteric, is not so uncommon as is usually believed, and can be diagnosed during the life of the patient by careful radiography of the skull. Obesity is present as a rule, and it resembles "the pituitary type of obesity" as seen in Cushing's disease. Hirsutism is most pronounced on the face, but in 2 of the author's cases it was absent. This syndrome should not be confined to the triad of symptoms described by Morel and Stewart; other subtle endocrine signs may be present, such as slight virilism, partial acromegaly, and mild insulin-resistant diabetes. The patients often complain of severe headaches. The condition progresses slowly, and in one case the hyperostosis was spontaneously arrested after 8 years. All the patients died from an intercurrent disease. Although at necropsy the changes seen on the internal surface of the frontal bones were very pronounced, no localized cortical signs of pressure were noted. Morgagni's syndrome is generally regarded as being caused by pituitary dysfunction, but the author thinks that there is not at present enough evidence to support this view, and in none of his cases were any pathological changes in the pituitary found. *J. T. Leyberg*

THYROID

2505. **Synthesis of Dihydromethylthiouracil. Comparison of its Antithyroid Action with that of Methylthiouracil.** (Synthèse du dihydro-méthyl-thiouracil et activité antithyroïdienne comparée à celle du méthyl-thiouracil)
G.-H. DELTOUR, D. BILLET, and C. MENTZER. *Annales d'Endocrinologie* [*Ann. Endocrinol., Paris*] **9**, 48–51, 1948. 1 fig., 4 refs.

Dihydromethylthiouracil was synthesized in an attempt to reduce the toxicity of methylthiouracil. Two methods of preparation were used; in one ethyl crotonate was heated with thiourea in a sealed tube for 10 hours at 140° C., while in the second the methylthiouracil was hydrogenated by sodium amalgam. In both cases the product had a melting point of 221° C. and closely resembled in physical properties the non-sulphur compound methyldihydrouracil.

The physiological activity was tested, doses varying from 0·052 to 6·4 mg. per 100 g. body weight being given either mixed with the diet or in drinking water made slightly alkaline. Each dose was tested on groups of 3 rats, kept in a constant temperature room, weighed every other day, and killed 10 days after the start of the experiment. Activity was estimated by increase in thyroid weight calculated as mg. of fresh tissue per 100 g. body weight and by decrease in concentration of total iodine in the thyroid gland estimated by the method of Michel and Lafon and expressed as mg. per 100 g. fresh tissue.

The results showed dihydromethylthiouracil to be less active as an antithyroid substance than methylthiouracil, the fall in total iodine concentration of the thyroid being much steeper in the case of the latter. Thus with a dose of 0·8 mg. dihydromethylthiouracil per 100 g. per day thyroid weight was increased from 15·6 mg. in the controls to 17·9 mg. and total iodine concentration was decreased from 55 mg. to 32·1 mg., whereas 0·76 mg. methylthiouracil increased thyroid weight to 23·5 mg. and reduced the iodine concentration to 7·7 mg. No comparison of the relative toxicity of the two compounds was made in the present study. *S. A. Simpson*

2506. **Appraisal of the Goitrogens. Results of Treatment with Thiouracil, Propylthiouracil and Related Antithyroid Drugs**
E. C. BARTELS. *Journal of Clinical Endocrinology* [*J. clin. Endocrinol.*] **8**, 766–775, Sept., 1948. 2 figs., 21 refs.

In this paper the author reviews previously published work on the drug treatment of thyrotoxicosis. The antithyroid drugs act by preventing the synthesis of organic iodine from the inorganic form. They are effective in reducing the basal metabolic rate in all cases of thyrotoxicosis. The claim that they are ineffective in thyrotoxicosis associated with acromegaly is not confirmed by the author's experience. He has pointed out that the basal metabolic rate may be raised in acromegaly without other clinical evidence of thyrotoxicosis. When thyrotoxicosis is present as a complication the thiouracil drugs will reduce the basal metabolic rate to a certain degree, and subsequent thyroidectomy will not reduce it further.

Propyl- and methyl-thiouracil appear to be the best preparations for clinical use and are effective in about the same doseages. An initial dose of 200 mg. per day is advocated for patients with primary hyperthyroidism and moderate-sized goitres, or 300 mg. per day for patients with large goitres due to either primary thyrotoxicosis or

adenomatous goitres. Both these drugs are less toxic than thiouracil, but cause toxic reactions in less than 2% of all cases treated. The author thinks that propylthiouracil will ultimately be proved to be less toxic than methylthiouracil. The thiouracil drugs should be used for all patients who are being prepared for subtotal thyroidectomy. Their use has reduced the mortality rate to 0·08%. The value of continued medical treatment is, however, still a matter for controversy. The incidence of prolonged remissions varies greatly from one clinic to another, and even though thyrotoxic symptoms are controlled the goitre remains or even continues to enlarge. *A. C. Crooke*

2507. **Goitrogenic Compounds: Pharmacological and Pathological Effects**
J. SEIFTER and W. E. EHRICH. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 303–314, March, 1948. 5 figs., 5 refs.

The authors tested 78 compounds for goitrogenic activity. The majority are chemical analogues of thiourea or of thiouracil, but some 30 compounds were examined because of their chemical relationship to other known goitrogens (cyano and aminophenyl compounds). The weight of the thyroid gland, its iodine content, and its microscopical appearance were regarded as criteria of goitrogenic activity; these criteria were found equally useful.

Propylthiouracil proved to be the most active of the compounds tested. Next came thiouracil and dithane, then 2-aminothiazole. Eight other substances were effective but much less active. Many of the compounds caused general disturbances, such as retardation of or arrest in growth of weanling white rats weighing 30 to 40 g., atrophy or necrosis of the thymus and other lymphatic structures, and degeneration of various excretory and endocrine glands. Experiments on starved animals showed that these general disturbances can be accounted for by the refusal of rats to eat an adulterated diet. *F. N. Fastier*

2508. **The Effect of Methylthiouracil on the Oxygen Consumption of the Thyroid, Liver and Kidneys**
U. BORELL and H. HOLMGREN. *Endocrinology* [*Endocrinology*] **42**, 427–435, June, 1948. 1 fig., 35 refs.

The mode of action of methylthiouracil in inhibiting thyroid secretion and causing hyperplasia of the thyroid gland was studied by measuring the respiratory quotient of the thyroid after methylthiouracil administration. The QO_2 of the liver and kidneys was also measured in an attempt to determine whether the action was restricted to the thyroid gland or whether other tissues were also affected.

Male albino rats kept on the same diet were given 0·1% methylthiouracil in drinking water. The animals were killed by decapitation 1 to 67 days after starting treatment and the oxygen consumption of the left thyroid lobe and of pieces of liver and kidney was determined by the Warburg technique. The QO_2 of the thyroid was increased 24 hours after methylthiouracil administration (controls −7·6, treated rats −9·5), maximal increase being found after 4 days (−11·4). A fall after 7 days' treatment (−8·4 at 30 days) was followed by an increase at 67 days (−11·7). In the liver there was a rapid fall from −11·8 in the controls to −10·2 24 hours after the start of treatment. The QO_2 continued to fall, the values remaining below those of the controls throughout the experiment. A similar result was obtained in the case of the kidney where a significant fall was found after 7 days' treatment, the value remaining low for the rest of the period of treatment. The authors consider that these results do not exclude the possibility that the mechanism is the same in all three cases, that is, interference with oxidation processes, the initial rise in oxygen consumption of the thyroid being due to an increase in cell volume rather than to a direct effect of methylthiouracil. This view is confirmed by Borell's previous findings that the QO_2 of the thyroid was increased after thyrotropin injection only during the 2 days when cell height was increased, and by the decrease which followed the initial rise in this experiment in spite of continued methylthiouracil administration. The increase found at 67 days is associated with glandular activity as shown histologically. Thyroid hormone synthesis was not entirely inhibited by methylthiouracil as shown by the slightly higher QO_2 values of the liver in animals treated with methylthiouracil than in thyroidectomized animals. Methylthiouracil was seen to have a direct effect on oxygen consumption by the liver, for the QO_2 of 5 out of 12 thyroidectomized rats treated for 4 days, starting on the 10th day after operation, was lower than that of untreated controls. No such effect could be seen in the case of the kidney. *S. A. Simpson*

2509. **Plasma Inorganic Iodide, a Chemical Regulator of Normal Thyroid Function**
J. WOLFF and I. L. CHAIKOFF. *Endocrinology* [*Endocrinology*] **42**, 468–471, June, 1948. 6 refs.

It has been suggested that thyroid hormone synthesis is governed by the level of iodine in plasma, no organic binding of the iodine occurring until the latter falls below a certain critical level; this level is reached chiefly by excretion of the excess through the kidneys. This view is supported by the results of injection of I^{127} labelled with I^{131} into nephrectomized rats. The rats received 10 μg. or 500 μg. I^{127} as potassium iodide 1 to 2 hours after recovery from anaesthesia and were killed 4, 10, 18, 26, 32, and 40 hours after injection. The plasma iodine level was estimated in blood obtained by heart puncture. The total iodine of the thyroid gland and the inorganic and organic fractions were determined.

After injection of 10 μg. the plasma iodine concentration remained at levels between 8 and 15 μg. per 100 ml. because there was no excretion by the kidneys. The amount of iodine in the gland increased from 0·8 μg. at 4 hours to 5·5 to 4·1 μg. at 32 hours. The percentage of inorganic iodine fell from a mean of 8 at 4 hours to 2 at 32 and 40 hours, whereas the organic fraction rose to 98% of the total iodine by 32 and 40 hours. After injection of 500 μg. the plasma iodine level remained

between 105 and 313 μg. throughout the 40-hour period. Of the total iodine found in the gland 74 to 99% was present as inorganic iodine whereas 26 hours after injection only 2% was present in the combined form, the highest value reached being 26% in one rat 40 hours after injection. Thus it appears that although the thyroid gland retained its ability to bind iodine after nephrectomy the high plasma iodine level maintained by this means inhibited the process. The response of thyrotoxic patients to iodine administration is probably similar, there being inhibition of thyroid hormone formation as a result of maintenance of a high level of plasma iodine.

S. A. Simpson

2510. **The Use of Radioactive Iodine in the Diagnosis of Thyroid Disease**

S. FEITELBERG, P. E. KAUNITZ, L. R. WASSERMAN, and S. B. YOHALEM. *American Journal of Medical Sciences* [*Amer. J. med. Sci.*] **216**, 129–135, Aug., 1948. 9 figs., 1 ref.

This report from the Mount Sinai Hospital, New York City, describes a method used to locate functioning thyroid tissue in the neck and elsewhere in 60 patients. Radioactive iodine (I^{131}) was administered by mouth, and 24 to 48 hours later measurements were made over the neck with a Sylvania γ-ray Geiger–Müller tube with a 5-inch collimator (aperture 1 inch (2·5 cm.), walls ½-inch lead). Measurements of activity were made at ½-inch intervals from the thyroid isthmus, both horizontally (laterally) and vertically. These measurements were then plotted on graphs as counts per minute against distance from the thyroid isthmus. The curve of the graph gave an indication of the distribution of the functioning thyroid tissue. Representative graphs and clinical histories are given of 7 cases of diffuse toxic goitre; lingual thyroid; non-toxic adenoma; haemorrhage into a colloid cyst (diminished uptake); lateral aberrant papillary adenoma; and carcinoma (2 cases, one of which showed uptake in metastases in the chest). It is concluded that this method is useful for preliminary studies, but should be supplemented by biopsy and radio-autographs.

G. Ansell

2511. **The Relationship of Hyperthyroidism to Myasthenia Gravis**

D. MCEACHERN and J. L. PARNELL. *Journal of Clinical Endocrinology* [*J. clin. Endocrinol.*] **8**, 842–850, Oct., 1948. 2 figs., 13 refs.

This paper reports 2 cases, both in adult women, of coexistent hyperthyroidism and myasthenia gravis. When the first patient was seen she had hyperthyroidism and only mild symptoms of myasthenia gravis. After subtotal thyroidectomy, however, the myasthenia became more severe and 15 mg. of neostigmine was required 4-hourly to control it. The second patient had symptoms of myasthenia gravis when first seen, and these were controlled by neostigmine. When she later developed symptoms of hyperthyroidism there was improvement in the myasthenic symptoms.

The inverse relationship between the two conditions was further illustrated by an increase in degree of the myasthenia gravis following first iodine and later thiouracil therapy, and by improvement when the iodine was stopped. Thyroid extract was given and produced improvement in the myasthenia gravis. The authors also comment on 6 other cases from the literature and discuss the relationship of these two conditions.

K. Black

2512. **Further Studies on the Antithyrotoxic Factor of Liver**

B. H. ERSHOFF. *Experimental Medicine and Surgery* [*Exp. Med. Surg.*] **6**, 438–446, Nov., 1948. 17 refs.

Immature rats fed on toxic doses of thyroid die early and show retardation in growth. Desiccated whole liver given orally to these rats prolongs their life and counteracts the retardation in growth. From experimental data it appears that the growth-promoting and survival-prolonging effects are due to different factors in the desiccated liver. The antithyrotoxic substance or substances of the liver is present in the water-insoluble and benzol-insoluble fractions of extracted liver residue, and is distinct from any other known nutrients, including vitamin B_{12}. There is some evidence (unpublished work) that other desiccated and defatted tissues such as kidney, heart, placenta, duodenum, thymus, or brain may have an antithyrotoxic effect. *A. I. Suchett-Kaye*

SUPRARENALS

2513. **The Effect of Desoxycorticosterone Acetate and Sodium Chloride in Orthostatic Anaemia and Postural Hypotension.** (Verkan av desoxycorticosteronacetat och koksalt vid ortostatisk anemi och postural hypotension) R. LUFT and B. SJÖGREN. *Nordisk Medicin* [*Nord. Med.*] **40**, 1764–1767, Oct. 1, 1948. 4 figs., 23 refs.

The authors recognize two types of orthostatic hypotension—arterial orthostatic anaemia and postural hypotension—in both of which the chief symptom is the inability to stand upright without giddiness. This is often accompanied by chronic fatigue and general asthenia.

In " arterial orthostatic anaemia " the normal fall in blood pressure on standing up is exaggerated; the systolic blood pressure falls although the diastolic does not, the pulse rate rises, and the electrocardiogram may show an increased P wave, a depressed S-T interval, and a depressed and inverted T wave. The condition is thought to be due to a disturbance of the balance between blood volume and volume or tone of the vascular system; contributing factors are poor vascular tone, pregnancy, large varicose veins, and a reduced blood volume. Ergotamine tartrate depresses the sympathetic vascular reflexes and makes the patient feel worse. " Postural hypotension " is a rare condition and due to organic nervous conditions, such as encephalitis, tumours, or softening, and has been reported in tabes, syringomyelia, and haematomyelia. When the patient stands up, systolic and diastolic pressures both fall but the pulse rate does not rise and there are no electrocardiographic changes. Autonomic vascular reflexes have been lost

and administration of ergotamine makes the patient feel better.

While studying the effect of desoxycorticosterone acetate and salt on the blood pressure, the authors successfully treated 2 cases in each of the above groups, 20 mg. " percorten " and 10 g. sodium chloride being given daily for a period of weeks. All patients became symptom free and resumed their activities, though desoxycorticosterone acetate administration had to be maintained. The drug was given by injection (suspension of 50 mg. every 2 weeks), by implants (5 tablets of 100 mg.), or by mouth (tablets of 5 mg. daily). In the cases of " arterial orthostatic anaemia ", the abnormal reaction on standing up disappeared and the resting blood pressure rose a little or entered the normal range. In " postural hypotension ", the abnormal reaction persisted but the resting blood pressure was raised to about 160/100 mm. Hg so that a fall produced no symptoms. The mechanism of the therapy is uncertain but desoxycorticosterone acetate and salt produce an increase in blood volume even in the absence of a rise in blood pressure, and this must certainly play some part. *A. M. M. Wilson*

2514. **Desoxycorticosterone and Changes in Carbohydrates and Electrolytes in the Liver.** (Desossicorticosterone e ricambi glicidico ed elettrolitico nel fegato) E. Tronchetti and E. Fiaschi. *Folia Endocrinologica* [*Folia endocrinol., Pisa*] **1**, 19–42, Oct., 1948. 8 figs., bibliography.

Verzár considers that adrenal cortical extract regulates cell metabolism by controlling the enzyme systems which promote phosphorylation. In his opinion intestinal or tissue absorption or utilization of carbohydrate and lipid molecules occurs only after preliminary phosphorylation. A significant movement of water and electrolytes is subordinated to the movement of carbohydrates and lipids for osmotic reasons. According to this concept the suprarenal cortex has the most important role in carbohydrate and lipid metabolism by control of phosphorylation and of changes in crystalloids and water in the osmotic regulation of tissues. Of the cortical steroids corticosterone is supposed to have a special influence on carbohydrate metabolism while to desoxycorticosterone is attributed a special influence on water and salt metabolism.

In this paper from the Medical Clinic of the University of Pisa the authors report experiments carried out to determine the relation of desoxycorticosterone to the metabolism of water, electrolytes, and carbohydrates. They used rabbits and injected into the portal vein: (1) glucose, 400 mg. in 1 ml. of water; (2) sodium chloride, 250 mg. in 1 ml. of water; (3) adrenaline $\frac{1}{20}$ mg.; (4) desoxycorticosterone, 1 and 2 mg. in 1 ml. of water; (5) desoxycorticosterone and glucose; (6) desoxycorticosterone and sodium chloride. Portal blood and suprahepatic blood samples were taken before these injections and 2, 5, 10, 15, and 20 minutes afterwards and blood sugar, chlorides, sodium, and potassium levels were determined together with haematocrit values. Results showed that in glycogenolysis chlorides and sodium are retained in the liver and potassium is liberated, while in glycogenogenesis potassium is retained and chlorides and sodium are liberated. The retention of potassium in the liver is explained by the authors by the attachment of this electrolyte to the hexosephosphate radicals during their change to glycogen. The movements of sodium and chlorides in the liver during glycogenolysis and glycogenogenesis correspond to the requirements of osmotic regulation. In contrast to total aqueous extract of suprarenal, desoxycorticosterone does not possess an immediate direct glycogenogenetic effect even in the presence of excess of glucose. Desoxycorticosterone mainly affects metabolism of water and chlorides in the liver; this may lead to secondary changes in glucose metabolism as above. *E. Forrai*

GENITAL GLANDS

2515. **Androgens and Renal Function. Effect of Testosterone Propionate in Uremia due to Cholera**
E. Henderson, H. Seneca, G. abd el Messih, and M. Weinberg. *Journal of Clinical Endocrinology* [*J. clin. Endocrinol.*] **8**, 851–865, Oct., 1948. 30 refs.

The authors review experimental evidence in favour of the theory that androgens affect renal structure and function. The experimental work suggested that some action might be demonstrable clinically. With this in mind they investigated the effect of administering testosterone to cholera patients with severe renal failure during the 1947 cholera epidemic in Egypt. In addition to the usual methods of treatment, 25 to 50 mg. of testosterone propionate was given daily to 40 patients with cholera complicated by uraemia, but dependable records could be kept in only 27 cases. Administration of testosterone was followed by an increase in the urinary output, usually within a few hours, and by a fall in the blood-urea level. Among the 27 cases which could be satisfactorily followed there were 5 deaths, a mortality of 18·5%, whereas the mortality rate in cholera patients with uraemia treated at the same hospital without testosterone was 70%. While recognizing the limitations of mortality statistics in such relatively small numbers of patients, the authors hope that their report will encourage further investigation into the use of testosterone propionate in diseases complicated by impaired renal function.
K. Black

2516. **So-called Virilism.** (О так называемом вирилзме)
N. A. Shereshevskii and E. A. Vasyukova. Клиническая Медицина [*Klin. Med., Mosk.*] **26**, No. 9, 17–30, 1948. 2 figs., 18 refs.

By virilism is understood a condition characterized by a masculine distribution of hair in women, together with masculine build and a masculine type of voice. It may be complicated by amenorrhoea and mental changes. It may occur by itself or as part of a more complicated syndrome—adrenal virilism.

The authors classify virilism as localized and generalized. They recognize 4 types. (1) A type not associated with any known endocrine disease: (*a*) a

form found in women in the Caucasus; (*b*) a hereditary constitutional form; (*c*) a form associated with brain tumours. (2) A type associated with functional changes in the endocrine system: (*a*) a rare form occurring during pregnancy; (*b*) a climacteric form. (3) A type associated with known pathological conditions of the endocrine system: (*a*) adrenal—adreno-genital syndrome of girls in childhood and adolescence, and tumours of the adrenal cortex in adults; (*b*) pituitary—Cushing's syndrome and acromegaly; (*c*) ovary—arrhenoblastoma and tumours of the corpus luteum; (*d*) pineal—Pellizzi's syndrome (macrogenitosomia praecox); (*e*) thyroid—in Graves's disease with concomitant atrophy of ovaries, and also in carcinoma of the thyroid. (4) A type associated with true or false hermaphroditism.

Taking these types of virilism one by one, the authors describe typical cases. Although they refer to the increase in excretion of testosterone in the adrenal and pituitary forms, they give no figures for this in their individual cases. In the former group, they found that many of the patients with the juvenile form of adreno-genital syndrome had adenomata of one or other adrenal, removal of which improved the condition though some of the symptoms remained. In one case the girl died a few hours after removal of an adenoma of the left adrenal, and at necropsy the right gland was found to be sclerosed—a danger to be borne in mind by operators. Out of 31 women with Cushing's syndrome, only one had well-marked virilism. The authors ascribe the virilism in such cases to secondary hypertrophy of the adrenals. Ovarian virilism they consider to be due to secretion of androgenic hormones by the arrhenoblastoma or other tumour. Cases associated with pineal or thyroid changes are regarded as being due to secondary adrenal hypertrophy.

[This account of virilism, based on the material available at the Institute of Experimental Endocrinology in Moscow, is marred by a complete absence of records of estimations of urinary sterols in any of the cases described. It therefore fails to add anything to our real knowledge of the aetiology of virilism in any of the pathological conditions dealt with.] *L. Firman-Edwards*

2517. **Turner's Syndrome in the Male. Report of a Case Showing Defects such as Short Stature, Sexual Under-development, Webbed Neck and Various other Congenital Defects without any Increased Urinary Pituitary Gonado-tropins**

G. B. DORFF, D. H. APPELMAN, and A. LIVESON. *Archives of Pediatrics* [*Arch. Pediat.*] **65**, 555–561, Oct., 1948. 2 figs., 15 refs.

In 1938 Turner described a syndrome of infantilism with congenital webbed neck and cubitus valgus. The condition has since been described exclusively in females, with one exception. In females the ovaries are rudimentary or absent, there is an increased excretion of urinary gonadotrophins, and other congenital defects such as coarctation of the aorta may be present.

The authors describe what is believed to be an example of Turner's syndrome in a male child aged 3 years. Mental development was normal. The boy was 33 in. (83·1 cm.) tall and weighed 26 lb. (11·7 kg.). Fontanelles were closed. There was slight bilateral proptosis and drooping of the upper eyelids. The nose was saddle-shaped, and the lower jaw underdeveloped with crowding of the teeth. The skin was coarse and dry, the hair of poor lustre but not coarse. There was a hairy naevus over the left sacral area, but no abnormal body hair elsewhere. " A congenital murmur was heard all over the praecordium ". [No further details of this are given.]

The testes were small and palpable in the inguinal canals. One testis could be pulled down into the scrotum. Congenital webbing of the skin from the mastoid process to the acromial process was present on both sides of the neck. There was a possible increase in the carrying angle (cubitus valgus). He had a moderate hypochromic anaemia. Further examination of the blood showed that levels of plasma proteins, fasting blood sugar, serum alkaline phosphatase, serum calcium and inorganic phosphorus, and serum cholesterol were all within normal limits. Radiographs of the skeleton showed a delay of about 6 months in carpal development. There was a spina bifida between the last lumbar and first sacral segments. No other bony abnormalities were seen. On two occasions the urine showed no abnormal increase in gonadotrophin (follicle-stimulating hormone) content.

The diagnosis from Klippel–Feil syndrome, from cretinism, and from hypopituitarism is briefly discussed. In this child it was not possible to say with certainty whether testicular agenesis was present. Too great a significance is not attached to the absence of urinary gonadotrophins, as an increase in excretion is not to be expected until puberty. *L. M. Rose*

2518. **Skeletal Effects of Estrogenic Hormone in Growing Vitamin C-depleted Guinea-pigs**

M. SILBERBERG and R. SILBERBERG. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 1019–1037, Sept., 1948. 12 figs., 14 refs.

Administration of oestrogenic hormone to growing guinea-pigs retards growth of epiphysial cartilage. The proliferating cartilage is narrowed, the calcified zone is widened, and there is an increase in the osseous trabeculation in the metaphysis. These changes progress until the animal (in about 5 weeks) becomes adapted to the hormone. If the animal is deprived of vitamin C during this period the development of scorbutic changes is delayed, but eventually these changes occur precipitously. Similarly the changes due to the sex hormone (including thickening of the arteries) are less pronounced if vitamin C is simultaneously withheld. *D. M. Pryce*

2519. **Intrinsic Testicular Syndromes.** (Sindromes testiculares intrinsecos)

A. ATRIA. *Revista Médica de Chile* [*Rev. méd. Chile*] **76**, 529–538, Sept., 1948. 6 figs., 25 refs.

The author divides his cases into three groups: (1) Albright's syndrome (*Trans. Ass. Amer. Phys.*, 1941, **56**, 43), in which both the spermatogenic and the interstitial tissues of the testis are affected, resulting in failure of

development of the secondary sexual characteristics and aspermia (pre-puberty functional castrates); the excretion of 17-ketosteroids is low but there is a compensatory increase in the excretion of gonadotrophic hormone. (2) Klinefelter's syndrome (*J. clin. Endocrinol.*, 1942, **2**, 615), in which the spermatogenic tissue suffers but the interstitial tissue is normal, and the clinical picture consists of gynaecomastia, testicular atrophy, and aspermia, with conservation of the secondary sexual characteristics; 17-ketosteroid excretion is normal but there is an increase in the output of prolan A. (3) Del Castillo's syndrome (*ibid.*, 1947, **7**, 493), in which the germinal epithelium is destroyed but the spermatogenic tissue and Leydig's cells are conserved; there is testicular atrophy with aspermia, though the secondary sexual characteristics are not affected. The excretion of 17-ketosteroids is reduced.

The author then proceeds to discuss the hormonal factors responsible for the different clinical pictures. In the first group there were 10 patients: 9 of these initially complained of poor genital development, 3 gave a history of mumps, and in 2 there was a familial tendency to eunuchoidism. The physical findings and clinical history are described. In the second group there were 4 patients, of whom 3 complained chiefly of gynaecomastia. The testes were small but libido was normal and sexual intercourse frequent. Sperms were absent from the seminal fluid. In the third group there were 2 patients, both of whom were under psychiatric treatment for impotence. One had had mumps. The general configuration was female in character. This group was obviously not so well demarcated as the other two. The author tends to regard trauma or inflammation as having no aetiological significance, but constitutional factors as being important. He refers to similar conditions resulting from deficiency in vitamins A and E.

In the first group, which was treated with chorionic gonadotrophic hormone, the results were poor. In the second group testosterone applied to the breasts had little effect; testosterone implants produced no significant change, and the author considers plastic operation the only choice. In the third group, which was treated with androgens, the impotence apparently disappeared.

[The treatment of such cases as these is obviously still very unsatisfactory.] *Paul B. Woolley*

2520. **Influence of Ultraviolet Rays on the Biological Activity of Oestrone.** (Influence des rayons U.-V. sur l'activité biologique de l'oestrone)
M. HERLANT and J. THOMAS. *Annales d'Endocrinologie* [*Ann. Endocrinol., Paris*] **9**, 12–19, 1948. 13 refs.

The claims of Figge were re-investigated; he stated that oestrone on irradiation with ultraviolet rays loses oestrogenic activity but has an increased potency for pituitary stimulation comparable to that claimed by Smith for Westerfeld's lactone. A solution containing 5 mg. crystalline oestrone dissolved in 0·5 ml. N/10 NaOH and 5 ml. ethyl alcohol was irradiated for 8 hours by a 600 watt quartz mercury vapour lamp. During irradiation the solution was placed in a crystallizing dish surrounded by ice at a distance of 11 cm. from the lamp. After irradiation the substance was either diluted with 100 ml. distilled water or evaporated and taken up in 5 ml. olive oil.

Irradiation caused loss of oestrogenic activity, no response being obtained in castrated mice given doses of 2·5 to 7·5 μg. of aqueous or oily solutions although untreated oestrone produced active vaginal smears in all mice injected with these doses. The effect on gonadotrophin secretion by the pituitary was tested in immature female rats. A single 100 μg. dose of untreated oestrone caused vaginal opening and cornification 24 hours after injection, whereas 100 μg. irradiated oestrone produced vaginal opening in 1 rat out of a group of 5. Two groups of rats injected with 50 μg. of untreated or irradiated oestrone with an 8 hour interval were killed 48 hours after the last injection. Uterine weight was increased in both groups but the increase was greater after untreated oestrone. Ovarian and adrenal weight was increased only in rats injected with untreated oestrone. No corpora lutea were found in any of the rats. These results were confirmed in a second experiment when 500 μg. irradiated oestrone in olive oil was injected over a period of 3 days and the rats were killed on the fifth day after the first injection. The authors conclude that irradiation did not increase the pituitary-stimulating potency of oestrone as neither gonadotrophin nor adrenotrophin secretion was increased, as shown by comparison with untreated oestrone. They consider the increase in uterine weight found in the immature rats to be due to residual oestrogenic activity. This was supported by the finding of increase in uterine weight in castrated rats after injection of 250 μg. aqueous and 500 μg. oily solution of irradiated oestrone. Moreover, irradiation for 12 hours caused almost complete destruction of oestrogenic activity, 500 μg. causing no significant increase in uterine or ovarian weight. Eight-hour irradiation of oestradiol and allenolic (Horeau's) acid caused no inactivation as judged by the effect of injection into ovariectomized mice. *S. A. Simpson*

2521. **Identification of Pregnanediol in the Urine of Two Subjects with Gynaecomastia: Its Value as a Test of Hyperfolliculinism in the Male.** (Identification du prégnandiol dans les urines de deux sujets atteints de gynécomastie: sa valeur comme test d'hyperfolliculinisme chez l'homme)
J. DECOURT, M. F. JAYLE, and J.-M. DOUMIC. *Annales d'Endocrinologie* [*Ann. Endocrinol., Paris*] **9**, 305–315, 1948. 4 figs., 6 refs.

Two cases of gynaecomastia are described. The first patient, a male student aged 19, had noted breast enlargement from the age of 15. The breasts were large and lobulated with enlarged, deeply pigmented nipples and areolae; they were slowly decreasing in size. Otherwise the patient was mentally, psychologically, and physically normal, though his pelvis was slightly enlarged. The second patient, a man aged 46, had suffered from gynaecomastia since puberty at the age of 14, and from obesity of feminine distribution for 28 years; pubic hair was of feminine distribution. His other characteristics and sexual activities were normal.

The excretion of 17-ketosteroids was 50 to 70% below the normal average in Case I but normal in Case II; total urinary steroid glucuronide content of urine was raised in both patients, phenol steroid content increased in Case II to 440 μg. and in one estimation in Case I to 350 μg., though never subsequently detected in this patient's urine. Pregnanediol glucuronide was excreted in amounts varying in Case I from 9 mg. to 21·5 mg. in 24 hours, and in Case II from 24·6 mg. to 43·5 mg. in 24 hours. In Case II the substance estimated as pregnanediol glucuronide was isolated and identified as such. Values for the excretion by normal men of 17-ketosteroids, total steroid glucuronides (acetone soluble and insoluble fractions) pregnanediol glucuronide (acetone insoluble fraction), and phenol steroids are given. The origin of the pregnanediol glucuronide isolated in the 2 cases described is discussed. *Walter H. H. Merivale*

2522. **Alteration of the Estrual Cycle in Sheep by Use of Progesterone and its Effect Upon Subsequent Ovulation and Fertility**
R. H. Dutt and L. E. Casida. *Endocrinology* [*Endocrinology*] **43**, 208–217, Oct., 1948. 11 refs.

Daily injections of 10 mg. of progesterone inhibited ovulation and heat in ewes. The injections were started 4, 8, or 12 days after the first day of oestrus (that is about 16, 12, and 8 days before the next expected heat) and continued for 14 days. When treatment was stopped all the ewes came into heat and ovulated within a week (on the average after 3·2 days). The ewes were mated at heat and the eggs were apparently fertile, since 67% of them were segmented when washed out of the Fallopian tubes. The result is explained by the hypothesis that progesterone inhibits the secretion of pituitary luteinizing hormone.

With a daily dose of 5 mg. of progesterone the inhibition was not so complete. Of 18 ewes only 12 showed heat and ovulation during the week after stopping treatment (the average interval was 2·8 days in these 12), and one ovulated but did not come on heat. Two of those that did not ovulate had cystic follicles and the other 3 had already ovulated during treatment. The failure of inhibition was commonest in the ewes in which treatment was started 12 days after oestrus. It is supposed that a daily dose of 5 mg. of progesterone when unsupplemented by endogenous progesterone is not large enough to prevent secretion of pituitary luteinizing hormone in ewes. *Peter C. Williams*

PITUITARY

2523. **Effects of Pituitary Adrenocorticotropic Hormone on the Intact Rat, with Special Reference to Cyto-chemical Changes in the Adrenal Cortex**
G. E. Bergner and H. W. Deane. *Endocrinology* [*Endocrinology*] **43**, 240–260, Oct., 1948. 22 figs., 40 refs.

The adrenocorticotrophin used in these experiments was uncontaminated with other anterior pituitary hormones but contained some pressor and oxytocic activity. When given to rats which fasted during the 24 hours of the experiment it produced involution of the thymus and depletion of the steroids in the adrenal within 6 hours. Cytochemical study by sudan staining, Schiff reagent, acetone solubility, and polarizing and fluorescence microscopy showed that the steroid depletion involved the fasciculate zone only; the steroids in the glomerular zone were unaffected. Later the adrenal cortex hypertrophied and the steroid content was partly restored; at the same time (after 18 to 24 hours' treatment) the liver glycogen was increased. During these short-term experiments the urinary excretion of chloride and nitrogen was increased (the increase in chloride perhaps being due to the posterior-pituitary contaminant).

When the hormone was given daily for 12 days to rats that were forcibly fed a constant diet, there was little difference from controls in urinary electrolyte excretion but urinary nitrogen output was much increased and there was a transient glycosuria during the first two days. The cytochemical study of the fasciculate zone indicated an increase in steroids during the earlier part of the 12 days but a beginning depletion by the end; these findings are equated with the resistant and exhaustion phases of the general adaptation syndrome.

The cytochemical tests are taken to warrant the conclusion that ketosteroids are concerned in the observed changes, which represent changes in the hormones of the adrenal cortex. In the short-term experiments these hormones are initially released rapidly from the fasciculate zone but later the rate of their production is increased to counterbalance this increased secretion; only in the longer experiments does this process show signs of becoming exhausted. There is no evidence that adrenocorticotrophin increases the output of the steroids affecting electrolyte balance; other evidence has already shown that these steroids are secreted by the glomerular zone. In this respect the rat differs from man, for the available clinical evidence suggests that adrenocorticotrophin increases the secretion of those adrenal steroids controlling electrolytes as well as those affecting sugar metabolism by stimulating gluconeogenesis.
Peter C. Williams

2524. **Metabolic Studies in Cushing's Syndrome. Treatment with Various Androgens and a Six-year Follow-up**
E. H. Keutmann, H. A. Friedman, S. H. Bassett, C. D. Kochakian, and E. M. Russ. *American Journal of Medicine* [*Amer. J. Med.*] **5**, 518–531, Oct., 1948. 5 figs., 37 refs.

The detailed clinical history of a girl with Cushing's syndrome due to basophilic hyperpituitarism, with excessive production of adrenocorticotrophic hormone is recorded. Administration of testosterone propionate resulted in an increase in strength and well-being, an improvement in mental outlook, and loss of pain due to spinal osteoporosis. Laboratory studies showed retention of nitrogen, phosphorus, and magnesium; diminished calcium loss; a rise in the basal metabolic rate towards normal; and improved absorption of glucose from the gastro-intestinal tract with consequent improved sugar tolerance. *Geoffrey McComas*

Dermatology

2525. **Topical and Parenteral Penicillin Therapy in Ritter's Disease. Report of Four Cases with Recovery**
R. O. WARTHEN and J. C. SHERBURNE. *Journal of Pediatrics* [*J. Pediat.*] **33**, 717–721, Dec., 1948. 12 refs.

The expected mortality rate in Ritter's disease is about 50%. Four cases are reported here, all with recovery after penicillin therapy. The authors consider that the causative factor is an irritant, either systemic or topical, and that there is a secondary coccal invasion. An account is given of the clinical signs of the disease and it is stressed that the most important therapeutic measure is the prevention of infection. To this end it is recommended that the infant should be kept warm by a heat cradle, be handled as little as possible, wear no clothes (not even a napkin), and have no baths, that the whole body should be kept covered and moist with penicillin ointment changed three or four times daily, and that penicillin should be given intramuscularly in doses of 50,000 units 3-hourly. This treatment should be continued for several days after recovery to avoid any possibility of recurrence. *W. F. Gaisford*

2526. **Dermatitis Resulting from Contact with Moths (Genus *Hylesia*). Report of Cases**
W. R. HILL, A. D. RUBENSTEIN, and J. KOVACS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 737–740, Nov. 6, 1948. 3 figs., 5 refs.

Dermatitis from contact with moths (genus *Hylesia*) is reported in 31 members of the crew of a vessel which had visited a port in Venezuela. The eruption was papulovesicular, morbilliform, or, occasionally, purpuric, and appeared on sites of contact. Relapses and new cases resulted when there had been contact with sheets in which moths had been imprisoned; patch tests were positive in one patient and 2 volunteers tested.

Similar eruptions have previously been described and the literature is reviewed. *John T. Ingram*

2527. **Acute Exfoliative Dermatitis and Death Following Penicillin Therapy**
J. RABINOVITCH and M. C. SNITKOFF. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 496–498, Oct. 16, 1948. 1 ref.

This appears to be the first recorded example of death due to penicillin administration. A woman of 72 was operated upon for acute appendicitis, a gangrenous appendix was removed, and penicillin was given because the peritoneal cavity contained turbid fluid, which yielded a non-haemolytic streptococcus on culture. The dose was 400,000 units daily in divided doses for 11 days. By then she had recovered completely, and the wound was healed. Seven days later her body was covered with an itching maculo-papular rash; diphenhydramine hydrochloride (" benadryl ") was given, but had no effect. Eventually she became covered with a fiery red bullous rash, in some places discharging a clear serous fluid. In spite of treatment, she became jaundiced, and died 13 days after the onset of symptoms. Two of the patient's children had also reacted violently to penicillin. The jaundice was probably due to a toxic hepatitis. The authors believe that the penicillin itself, and not impurities, caused the reaction, for three members of the same family had suffered from rashes after different batches of the drug; they emphasize the importance of performing scratch tests, especially where there is a family history of allergy, as the amount of drug given seems to have nothing to do with the severity of reaction. *T. E. C. Early*

2528. **Contact-type Sensitization to Antibiotic Agents**
M. BERKE and M. E. OBERMAYER. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 253–258, Oct., 1948. 5 refs.

Patch tests with streptomycin, penicillin, tyrothricin, and procaine hydrochloride were carried out on 51 nurses who had previously handled streptomycin. The tests showed that streptomycin was an important contact-type sensitizing agent, and that procaine hydrochloride used concomitantly with streptomycin was a major factor in the causation of eczematous dermatitis. *G. B. Mitchell-Heggs*

2529. **Mycosis Fungoides**
E. K. STRATTON. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 307, Nov., 1948. 1 ref.

The author submits evidence to show that mycosis fungoides is probably due to a toxin or a virus; he therefore suggests that the disease is not a form of neoplasm. Since 1942 he has succeeded in 3 out of 4 cases in producing a disease in mice which, on microscopical examination of material obtained at necropsy, appeared to be identical with mycosis fungoides. The disease was transmitted to mice by tissue passage and by " cell free " emulsion. In one instance, tissue emulsion was inoculated on to the chorio-allantoic membrane of an egg and the embryo developed tumours on the eye and in the heart. *R. M. B. MacKenna*

2530. **Experimental Inoculation of the Rabbit with Nodules of Mycosis Fungoides.** (Esperimenti d'inoculazione nel coniglio di nodi della " Micosis fungoides ")
R. LEONE. *Giornale Italiano di Dermatologia e Sifilologia* [*G. ital. Derm. Sif.*] **89**, 349–362, July–Aug., 1948. 3 figs.

Sterile suspensions of non-ulcerated nodules from 2 cases of mycosis fungoides were injected into rabbits by

the endocerebral route. The rabbits developed spastic paresis of the limbs and some of them died. Necropsy revealed encephalitis with widespread degeneration of nerve cells in the cortex. Fragments of the brain of these rabbits were transferred into other rabbits by the same route. No encephalitis developed. The authors believe that the encephalitis in the first series of animals was due to the transfer of a virus. [They do not explain, however, why the virus could not be transferred to the animals of the next series or why it failed to cause the paresis after the first passage.] *Kate Maunsell*

2531. **Results Obtained in the Treatment of Kaposi's Sarcoma with Penicillin. Preliminary Communication.** (Resultados obtenidos en el tratamiento de la sarcomatosis de Kaposi por la penicilina. Comunicacion previa)
L. PIERINI and D. GRINSPAN. *Revista Argentina de Dermatosifilologia* [*Rev. argent. Dermatosif.*] **32**, 3–14, Jan.–June, 1948. 15 figs.

A detailed description of 2 cases is given in which the duration of the disease was 7 and 8 years respectively. Both patients were treated with 5,000,000 units of penicillin at a 4-hourly rate of 50,000 units. There was a definite regression of the lesions, confirmed histologically. The tumoral and the pediculated formations shrank and dried up; many of the latter fell off spontaneously, leaving a pigmented spot at the site of insertion. The cases were followed up for 3 and 5 months respectively and no tendency to relapse was noted. Although spontaneous regressions of Kaposi's sarcomata are known to occur, the rapid response to the treatment in both cases can hardly be ascribed to a coincidence. The result of penicillin treatment in a third case—of a man aged 83, with extensive lesions of 12 years' duration and in bad general health—was unsatisfactory.

A. Lilker

2532. **Further Studies on the Treatment of Lupus Erythematosus with Sodium *para*-Aminobenzoate**
C. J. D. ZARAFONETIS, R. H. GREKIN, and A. C. CURTIS. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 359–381, Nov., 1948. 6 figs., 13 refs.

para-Aminobenzoic acid in the form of sodium *para*-aminobenzoate was administered by mouth in doses of 2 to 4 g. every 2 to 3 hours to 18 patients suffering from lupus erythematosus while they were in hospital. Of 6 patients with chronic discoid lupus erythematosus 2 failed to improve. All 6 with chronic disseminated lupus erythematosus derived benefit while taking the drug but relapsed on its withdrawal. Of 5 cases of subacute disseminated lupus erythematosus 4 showed similar benefit. The fifth patient, a child of 4 years of age, died of toxic hepatitis. One patient with acute disseminated lupus erythematosus died after one week. Biopsy specimens from patients who had benefited showed a marked diminution of round-cell infiltration during treatment. Toxic effects—nausea, vomiting, pruritus, drug rash, and drug fever—were encountered. All patients taking 18 g. or more of sodium *para*-aminobenzoate daily had renal glycosuria. Discussion of the paper, which was read before a meeting of the Society of Investigative Dermatology, Chicago, was critical and not very encouraging. *J. E. M. Wigley*

2533. **The Mechanism of Urtication in Urticaria Pigmentosa**
T. S. SAUNDERS and O. G. MILLER. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 309–310, Nov., 1948. 2 refs.

It has for long been suspected that the urtication caused by rubbing the lesions of urticaria pigmentosa was due to the traumatic liberation of histamine-like substances in the skin. The authors considered that if this was true, urtication could be inhibited by the use of histamine antagonists. They report the details of an investigation in a case of urticaria pigmentosa in which factitious urticaria was not prevented by the administration of antihistamine drugs locally or by ingestion, but was completely inhibited by intravenous injection of 25 mg. of " benadryl ". They therefore conclude that the original hypothesis is probably correct. They note that an attempt to demonstrate a " dermographism-inducing-principle " in the patient's blood by the method of passive transfer was unsuccessful.

R. M. B. MacKenna

2534. **Experiences in the Treatment of Lupus with Vitamin D_2.** (Erfahrungen über die Lupusbehandlung mit Vitamin D_2)
R. LENGGENHAGER. *Dermatologica* [*Dermatologica, Basel*] **97**, 40–49, 1948. 6 refs.

A report is given on the vitamin D_2 therapy of lupus at the dermatological clinic of Zürich. Most of the 83 cases analysed were followed up for over a year. The treatment consisted of oral administration of 150,000 units vitamin D_2 (in tablet form) daily for 2 months, and 100,000 units vitamin D_2 daily for the following months. After about 6 months, 12% of cases with skin manifestations, and 40% of those with mucous membrane involvement, were clinically cured. After one year a total of 50% appeared to be cured. Only patients with at least 5 months' treatment were included in this series. Eleven relapses were seen and occurred most commonly after a year. Histological examination of 20 cases revealed satisfactory healing only in 2, non-specific inflammatory changes in 3, and tuberculous structures in the skin of 15. It is emphasized that of this latter group 3 patients appeared to be clinically cured. In 23 out of 82 cases, some toxic reactions to the drug were observed—nausea at the beginning of treatment in 14 cases, thirst or polyuria in 4 cases, and metallic taste in 1 case. In 4 cases the treatment had to be discontinued because of intolerance. The serum calcium level was markedly raised in only 7 cases. In patients who also had pulmonary tuberculosis, the vitamin D_2 therapy had no beneficial action on the lung condition and may have aggravated it in 2 of them. In these 2 cases, however, the condition of the lungs was not known before treatment.

The author considers, therefore, that in all cases a

search for visceral tuberculosis should be made before treatment, and every 3 months during therapy. It is suggested that a demineralization of calcified tuberculous foci may occur, thus rendering radiological control absolutely necessary. *G. W. Csonka*

2535. **Vitamin D_2 Treatment of Cutaneous Tuberculosis (152 Observations.)** (Terapia con vitamina D_2 nella tubercolosi cutanea. Su 152 casi d'osservazione)
R. CAVALIERI. *Dermosifilografo* [*Dermosifilografo*] **23**, 191–250, Aug., 1948. 18 figs., bibliography.

Some 152 patients suffering from various types of tuberculosis of the skin were treated with vitamin D_2 (calciferol); 110 of the patients suffered from lupus vulgaris. Amongst the remaining 42 were patients suffering from tuberculous ulcers, lymph-node tuberculosis, tuberculides, lupus erythematosus, and various other skin conditions. Vitamin D_2, 30 mg., was given thrice weekly during the first 2 weeks and twice weekly during the following month, making a total of 420 mg. (16,800,000 i.u.). This was estimated as the " curative dose " and was followed by a " maintenance dose " of 30 mg. per week, an attempt being made to give this dose for a year.

The author states that practically all the patients with lupus vulgaris were cured. Only a small proportion of patients received local treatment as well. Other forms of cutaneous tuberculosis responded less favourably. Acne and psoriasis did not respond at all. Relapses occurred mainly in those patients who did not continue with treatment for longer than 5 months. Serious side-effects from these massive doses were reported only in 3 pregnant women. *Kate Maunsell*

2536. **Seasonal Variations in the Occurrence of Impetigo Contagiosa.** (Sæsonvariationer ved impetigo contagiosa)
E. SYLVEST. *Nordisk Medicin* [*Nord. med.*] **40**, 1926–1929, Oct. 22, 1948. 1 fig., 8 refs.

An analysis of a series of 508 cases of impetigo contagiosa extending over a period of 10 years revealed seasonal variations and a characteristic age distribution. It was found that 237 of the cases occurred in September and October, and a further 155 in August and November, making 392 cases in the late summer and autumn. Only 5 cases out of 492 occurred in infants under 1 year; the majority of the remainder—that is, 411—were seen in children under the age of 14. Of the children affected 64% were boys. Very few cases indeed occurred in subjects over the age of 30. *B. Nordin*

2537. **Accidental Vaccination: A Cause of Confusion in the Diagnosis of Lesions of the Lip and Penis**
L. L. CORIELL, H. BLANK, and T. F. MCN. SCOTT. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 313–321, Nov., 1948. 4 figs., 10 refs.

Two unusual cases in negro children are described. In the first case a 3-year-old boy presented a lesion simulating a primary syphilitic chancre on the penis; in the second case a somewhat similar lesion developed on the lower lip of a 10-year-old girl. The authors describe the laboratory studies, which established the diagnosis of accidental vaccination. In the discussion they state that the procedures applicable to the diagnosis of vaccinia are the same as those used in the diagnosis of other virus diseases: (1) the clinical history and findings; (2) the isolation and identification of the causative agent; (3) demonstration of a specific immunological response of the patient to virus, and (4) demonstration of a specific histological change in the tissues of the infected patient or experimental animal. They believe that if any two of these criteria are satisfied the diagnosis is established. [The paper contains many technical details which are of interest to those with special knowledge of virus procedures.] *R. M. B. MacKenna*

2538. **Latent Bone Lesions in Patients with Lupus Vulgaris.** (Скрытые поражения костей у больных туберкулезной волчанкой)
I. N. AGAPKIN. Проблемы Туберкулеза [*Probl. Tuberk.*] No. 6, 32–38, Nov.–Dec., 1948. 17 refs.

Lupus vulgaris, which is due to haematogenous tuberculous infection, is frequently accompanied by a tuberculous infection of the bones and joints. The skeletal lesions may be obvious, but in a number of cases they may be latent and can only be detected by *x* rays. In such cases they appear as limited dense or sclerosed foci in the bone. *A. Orley*

2539. **Ringworm of the Scalp**
R. T. BEHLING and I. J. MARKEL. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 239–242, Oct., 1948. 1 ref.

An epidemic of ringworm of the scalp in a city of 5,810 school children, 431 of whom developed the condition, was controlled by local applications. An ointment containing 5% salicylanilide or a liquid containing 10% copper undecylenate was used. The methods employed and the many factors essential to the success of the treatment are fully discussed.
G. B. Mitchell-Heggs

2540. **Histologic Examinations of Fungous Infections of the Nails**
F. SAGHER. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **11**, 337–357, Nov., 1948. 7 figs., 51 refs.

According to the authors, " the systemic histologic examination is a diagnostic procedure which has not been generally employed in studying nails infected by fungi ". As a result of such examination of nails from 14 patients, different types of fungus were found to damage nails in different degrees and manner. The finding of fungi in a potassium hydroxide preparation of scrapings was not always considered enough to establish the diagnosis of onychomycosis. It was concluded that histological examinations may well prove helpful in " indicating suitable treatment for different types of fungous infections of the nail ". *J. E. M. Wigley*

Venereal Diseases

2541. **The Treatment of Late Symptomatic Neurosyphilis at the Boston Psychopathic Hospital. A Study of the Results of Penicillin Therapy in 394 Patients Treated Between February, 1944 and March, 1948**
I. KOPP, A. S. ROSE, and H. C. SOLOMON. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [*Amer. J. Syph.*] **32**, 509–520, Nov., 1948. 4 figs.

Between February, 1944, and March, 1948, the authors treated 394 patients with neurosyphilis, of whom 305 had general paresis (G.P.I.). Of the 305, 140 had simple dementia, 55 were schizoid, 25 grandiose, 23 manic-depressive, and 2 psychoneurotic and 60 had no psychosis; there were 31 deaths within 24 months, 16 of which (4%) were due to G.P.I. Treatment consisted of administration of 3,000,000 or 6,000,000 units of penicillin over 5 to 15 days with or without fever therapy; fever therapy was about half that normally employed, that is, 5 to 7 paroxysms of malaria or 20 hours in a fever cabinet. Of the 305 patients followed up for 3 months or more 170 (54%) were improved, 104 (34%) were not improved, and 31 (10%) died. The figure for clinical improvement increased during the first year to 70%; the following were the percentages for the various types of G.P.I.: manic-depressive 90, grandiose 65, simple dementia 60, schizoid 25, and without psychosis 85. When penicillin in either dosage was given over 5 to 10 days improvement occurred in 50%, when over 15 days in 71 to 72%; on the other hand re-treatment was necessary more often after 3,000,000 than after 6,000,000 units of penicillin and more often when penicillin was given alone than when it was given together with fever therapy. In the spinal fluid, the maximum fall in cell count and protein content occurred at 18 months, figures for the gold sol reaction fell progressively for 36 months, and the Wassermann reaction weakened gradually but most rapidly during the first 9 months. Of 188 samples of fluid, 19% were negative or nearly so 12 to 14 months after treatment; it made little difference whether 3,000,000 or 6,000,000 units of penicillin had been given. It is concluded that administration of 6,000,000 units of penicillin over 15 days combined with moderate fever therapy constitutes the most effective treatment for late symptomatic neurosyphilis. *T. E. Osmond*

2542. **Long-term Results in Neurosyphilis Treated with Penicillin Alone**
J. H. STOKES, M. S. FALK, and G. D. GAMMON. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [*Amer. J. Syph.*] **32**, 521–545, Nov., 1948. 6 figs., 3 refs.

This is the fourth of a series of annual reports on the treatment of neurosyphilis with penicillin alone; spinal fluid normality and "near-normality" were maintained in 47 and 19% of cases respectively; during the fourth year the proportion of "marked improvement" increased from 18 to 25%. Three graphs show that few patients with asymptomatic neurosyphilis achieve a normal or nearly normal spinal fluid; in a few cases there is failure or relapse, but initial failure does not rule out final success; in paresis and tabo-paresis the prognosis is poorer but cases tend to improve with time and the incidence of relapse in the spinal fluid is low; in tabes abnormal spinal fluid responds rapidly and completely. The percentages of normal or nearly normal fluid after 2 years or more in the various types of neurosyphilis are as follows: paresis 46, tabo-paresis 60, meningo-vascular syphilis 60, asymptomatic syphilis 74, and tabes 80. Seventeen case histories are given in detail; these bring out various characteristics of the different types of response to penicillin and to more time-honoured methods of treating each type of neurosyphilis; one striking feature is the frequent failure to reduce the number of reagin units in the blood, even when spinal fluid changes show great improvement. In one case of meningo-vascular syphilis, 12 injections of arsphenamine, 86 of bismuth, and 91 of tryparsamide had no effect; 14·4 mega units of penicillin elicited a marked response but this was followed by a relapse; in another, 1·2 mega units accomplished as much as 14 Swift–Ellis treatments and 34 bismuth injections; in two cases Herxheimer reactions were rather severe. It is concluded that in all types of neurosyphilis penicillin is superior to other forms of treatment and is safer as well. [No comparison is made between results of penicillin alone and of penicillin combined with fever therapy.] *T. E. Osmond*

2543. **Treatment of Early Syphilis with Sodium Penicillin. A Preliminary Report with a Comparison of Results with 4,800,000 Units, Administered in Seven and a Half Days, with Smaller Dosage**
J. Q. BLACKWOOD, V. SCOTT, and E. G. CLARK. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph., Chicago*] **57**, 1028–1041, June, 1948. 4 figs.

The value of penicillin in syphilis is well established but the optimum dosage remains to be agreed. Early studies indicated that dosage should be greater than 2,400,000 units, and further investigations have been directed toward determining the result of: (*a*) utilizing larger total dosages, and (*b*) prolonging the duration of treatment. The present paper reports the preliminary results in 123 cases of syphilis diagnosed by dark-field examination treated with 4,800,000 units of commercial sodium penicillin in 7½ days (96 intramuscular injections of 50,000 units at 2-hourly intervals). At the end of 11 months of observation, the cumulative percentage of treatment failures was approximately 17, and comparison of this series with other studies previously reported indicates that these results are no better than those obtained with 1,200,000 and 2,400,000 units over 7½ days. The work of Eagle and his associates on

syphilis in rabbits has demonstrated the importance of the duration of treatment in relation to the dosage employed and the results in the present paper in syphilis in human subjects again underline the significance of the time–dose relationship. [This paper is a model for carrying out comparative studies of different treatment schedules and should be read in full.] *S. M. Laird*

2544. **Penicillin in the Treatment of Experimental Syphilis of Rabbits. IV. The Synergistic or Additive Activity of Penicillin by Oral Administration with Oxophenarsine Hydrochloride ("Mapharsen") by Intravenous and Intramuscular Injection and Bismuth Salicylate by Intramuscular Injection**

J. A. KOLMER. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph., Chicago*] **57**, 965–974, June, 1948. 5 refs.

An additive or synergistic effect had previously been demonstrated in experimental syphilis in rabbits when oxophenarsine hydrochloride intravenously or a bismuth compound intramuscularly was combined with penicillin given by intramuscular injection. The present paper describes experiments which show that a similar synergistic action occurs when the penicillin is administered by the oral route. The latter route is not recommended for the treatment of early syphilis in human beings, but the author suggests its trial in patients with congenital and late acquired syphilis. He also believes that intramuscular injection of oxophenarsine hydrochloride suspended in peanut oil or peanut oil and wax is more potent than sulpharsphenamine in the treatment of congenital syphilis in infants and young children or of adults in whom intravenous injection is technically difficult. *S. M. Laird*

2545. **Clinical and Histological Observations During Penicillin Therapy of Syphilis.** (Клинические и гистопатологические наблюдения при пенициллинотерапии сифилиса)

V. Y. ARUTYUNOV, E. I. GURVICH, and A. V. ILINA. Вестник венерологии и дерматологии [*Vestn. Vener. Derm.*] No. 6, 11–17, Nov–Dec., 1948. 4 figs.

The following therapeutic procedure was used in cases of syphilis: (*a*) each patient received 3-hourly intramuscular injections of 40,000 units of penicillin, the total dose being from 1,200,000 to 3,400,000 units; (*b*) the patient was then given, without any interval, 6 g. of neoarsphenamine in a daily dose of 0·15 g., and a total of 45 to 50 g. of "biochinol" (a preparation of quinine iodo-bismuthate). This course was completed in 80 to 90 days and was given to 100 men and women; ages and diagnoses are given in detail. In addition, a group of 34 patients were treated with penicillin alone, 3,400,000 units in 8 days. Most patients tolerated the therapy well; in one case of primary serum-positive syphilis, delirium developed after injections of 500,000 units of penicillin; necropsy revealed an acute cerebral oedema. On the average, *Treponema pallidum* disappeared from the chancre in 12 to 16 hours after intramuscular administration of 120,000 to 160,000 units of penicillin. The papules and pustules underwent involution in 10 to 12 days; these lesions, in some cases of fresh syphilis, disappeared in 5 to 6 days. Among the patients given a combined course of treatment, the serological reactions were usually negative towards the end of the course; out of 134 patients clinical relapse appeared in 5 and serological relapse in 3 during the 18 months after the termination of both types of therapy; two of the relapses were in patients treated with penicillin alone. Histological studies were made of material obtained from 50 biopsies. Findings in 6 representative cases (of primary and secondary syphilis and of relapse) are described in detail. In all samples there was regression of the syphilitic lesions; penicillin, though enhancing and accelerating the process of healing and absorption, never brought about a complete involution recognizable histologically. It is considered that further clinical tests and post-treatment observation extending over 10 to 15 years will be needed to appraise the values of treatment with penicillin alone and by the combined method.

H. P. Fox

2546. **The Serologic Relationships Between Five Cultured Strains of Supposed *T. pallidum* (Noguchi, Kroó, Nichols, Reiter, and Kazan) and Two Strains of Mouth Treponemata**

H. EAGLE and F. G. GERMUTH. *Journal of Immunology* [*J. Immunol.*] **60**, 223–239, Oct., 1948. 20 refs.

Five strains of treponema that have lost, during repeated subulture, any pathogenicity they ever possessed, were examined by agglutination and complement-fixation tests for comparison with *Treponema pallidum*. Two strains (Nichols and Noguchi) were serologically indistinguishable. Two strains (Kazan and Reiter) cross-reacted but were not identical. Reiter strain is serologically almost identical with two strains of saprophytic mouth treponemata. One strain (Kroó) was serologically distinct from the other four. Rabbits injected with any of these four strains developed agglutinating and complement-fixing antibodies, but no Wassermann or flocculating antibodies. Syphilitic sera absorbed with suspensions of the Reiter and Kazan strains lost all power to react with these organisms, but retained all Wassermann and flocculating activity. Immunization of rabbits with any of these four strains conferred on them no immunity to infection with *T. pallidum*.

On these grounds the authors consider that strains Nichols, Noguchi, Kazan, Reiter, and Kroó, are not, and probably never were, *T. pallidum*. *C. L. Oakley*

2547. **Erythema of the Ninth Day.** [In English]

F. REYMANN. *Acta Dermato-Venereologica* [*Acta derm.-venereol., Stockh.*] **28**, 238–255, 1948. 9 figs., 9 refs.

In the author's experience what has been termed ninth-day erythema develops between the seventh and fourteenth days after the first injection of arsenic and is independent of the second injection. A rise in temperature preceded the rash, but occasionally the high temperature occurred alone. A considerable number of patients complained of "sore throat" and had evidence of mild

pharyngitis. One had symptoms suggesting an " acute abdomen " which subsided spontaneously. Another, a non-syphilitic patient, developed a rise in temperature with acute abdominal pain on the seventh day after an injection of neoarsphenamine. This patient had previously had a haemolytic streptococcal pharyngitis and the antistreptolysin titre in the blood was rising. A certain accumulation of cases was noted, and on one occasion an epidemic was observed in a ward. Though streptococci were demonstrated in a fair proportion of cases, the presence of this organism was not universal. The sore throat preceded the rash by one day. Two cases of haemorrhagic encephalopathy were included in this series, in both of which the symptoms started 9 days after the first neoarsphenamine injection; in one case the condition was accompanied by a morbilliform rash. As an explanation of ninth-day erythema it is thought that a latent infection—for example, streptococcal—is activated by the first injection of neoarsphenamine.

[This paper is not very convincing, and it does not explain why the eruption should appear about the ninth day. The " epidemic " mentioned was too small to be significant, only 3 people being affected.]

G. W. Csonka

2548. **Spinal Fluid and Blood Complement Fixation Reversal in Neurosyphilis**

Y. T. Wong and H. Packer. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [*Amer. J. Syph.*] **32**, 565–573, Nov., 1948. 8 refs.

The authors investigated the extent to which a reversal of positive Kolmer complement-fixation tests with spinal fluid and blood occurs after treatment of neurosyphilitic patients with penicillin or penicillin and malaria.

The series of 120 comprised 70 cases of paresis and tabo-paresis, 21 of tabes dorsalis, and 29 of meningo-vascular syphilis. Penicillin alone, 30,000 units every 3 hours by day and night to a total of 2,400,000 to 6,000,000 units, was given to 56 patients. Penicillin together with malaria was given to 64 patients; the average number of hours of the duration of fever above 103° F. (39·4° C.) was 39·5. Reversal of previously positive reactions in the cerebrospinal fluid was recorded when the result was 1+ or less in 1 ml. of spinal fluid. In the blood a negative or doubtful result in a dilution of serum of 1 to 2·5 was taken as constituting reversal. The patients were observed over a period amounting in some cases to 3 years, the average period for the group being 18·9 months.

In the series as a whole in 88·9% the result was reversed in the cerebrospinal fluid within 18 months of treatment. The repeated tests show little difference as regards frequency of reversal between the cases of paresis and those of tabes (about 23% in each group); among the cases of meningo-vascular syphilis reversal was much more frequent (51·7%). The trend towards reversal was slower in the blood than in the cerebrospinal fluid. Some of the patients had been treated previously with arsenicals and bismuth during a 6-month period and in these a higher proportion (37·1%) of satisfactory results was noted.

This striking difference in favour of penicillin alone is thought to be due to the selection of patients, but even so the authors consider that penicillin alone is at least as effective as penicillin together with malaria for most types of neurosyphilis.

V. E. Lloyd

2549. **Syphilitic Primary Optic Atrophy as a Cause of Blindness; Importance of Early Diagnosis**

J. V. Klauder, G. P. Meyer, and B. A. Gross. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [*Amer. J. Syph.*] **32**, 574–586, Nov., 1948. 3 figs., 14 refs.

Primary optic atrophy accounts for 90% of blindness due to syphilis and it is believed that in the United States there are at least 50,000 cases at any one time.

The authors present a study of 397 patients with syphilitic primary optic atrophy; in only 20 cases was the infection of congenital origin. The great majority of the cases of acquired syphilis were in males, 315 in contrast to only 62 in females. Of the 20 patients with congenital syphilis, however, 14 were of the female sex. In the series 55% of patients had tabes, 25% meningo-vascular syphilis, 15% tabo-paresis, and 5% general paresis. The first complaint of failing vision was usually made between the ages of 40 and 50 years. The majority of patients had received no treatment in the early stage of the infection, and few, if any, had received treatment in amounts considered adequate according to modern standards. In many of the patients the underlying neurosyphilis ran a silent course and impaired vision was the first and only symptom. Other early symptoms included pains in the legs, transient diplopia, impaired adaptation to light, and difficulty in distinguishing colours.

The most constant signs found in the series in addition to optic atrophy were positive tests for syphilis in the blood and cerebrospinal fluid and pupillary abnormalities, namely, inequality, irregularity, sluggish reaction to light, Argyll Robertson pupils, or fixed pupils. The history of poor vision varied from a few weeks or months to years; some patients became blind in a year or less. The progression of optic atrophy and the degree of visual failure were often serious before the patient became aware of the impairment. Methods of ophthalmic diagnosis are discussed. The authors believe that a defect in the visual field usually precedes loss of central vision or pallor of the optic disk and is the earliest symptom of optic atrophy. A visual field defect as an isolated finding in a patient with syphilis is suggestive of the beginning of optic atrophy. The histories and progress of selected cases, together with visual field charts, are recorded.

The authors comment adversely upon the delay in the diagnosis of syphilitic optic atrophy in their cases; 61% of the patients when first seen were either " industrially " blind or had a visual acuity of less than 1/60. They recommend that the ophthalmoscope and the perimeter should be part of the equipment of every syphilis clinic, and that every patient suffering from neurosyphilis should be examined ophthalmologically.

V. E. Lloyd

Genito-Urinary Disorders

2550. **Chyluria: A Report of Ten Cases**
A. H. LOGAN, H. L. SMITH, and T. L. POOL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **216**, 389–396, Oct., 1948. 1 fig., 22 refs.

The authors, after briefly discussing the aetiology, pathogenesis, and treatment of chyluria, describe 10 cases seen at the Mayo Clinic. The patients were adults, aged 30 to 64 years, who gave a history of passing milky urine; otherwise there were no significant signs or symptoms. Retrograde pyelogram in 4 cases is said to have shown either " pyelolymphatic " or " pyelovenous " backflow, but it is not stated how these are demonstrated. All the cases were of the non-parasitic type, and detailed investigations failed to throw any light on the exact causation of the condition. *S. Karani*

2551. **Experimental Renal Injury due to Uranium.** (La nefropatia experimental por el uranio)
R. PICATOSTE, C. JIMÉNEZ DÍAZ, E. LÓPEZ GARCÍA, and M. MORALES PLEGUEZUELO. *Revista Clínica Española* [*Rev. clín. esp.*] **31**, 150–165, NOV. 15, 1948. 20 figs., 24 refs.

Uranium salts have been used since the last century to produce experimental nephritis, and the histopathological changes in the kidney are well known. The present authors gave uranium nitrate to a series of rats in doses ranging from 1 to 6 mg. per kilo body weight. Most of the animals survived the 1-mg. dose and, in confirmation of Suzuki's findings, became immune to doses as high as 10 mg. of uranium nitrate per kilo. Doses of 2 mg. per kilo upwards produced acute nephritis and death 5 to 13 days later.

Of considerable interest is an incidental finding that after a unilateral nephrectomy during the acute stage in cases of moderate intoxication (up to 2 mg. per kilo) the animals survive and become immune to higher doses. This phenomenon is tentatively ascribed by the authors to improved function of the remaining kidney, so that occlusion of the tubules is prevented. *A. Lilker*

2552. **Renal Response to Thermal Stimulus**
L. D. ODELL, G. T. ARAGON, and R. C. SMITTER. *American Journal of Obstetrics and Gynecology* [*Amer. J. Obstet. Gynec.*] **56**, 835–845, Nov., 1948. 7 figs., 20 refs.

The authors investigated the effects of cold on the blood pressure and urine excretion in 66 subjects. Of these patients 22 had toxaemia of pregnancy [the exact meaning of this wide term is not defined]; 33 were studied during normal pregnancy; one had a glioma of the spinal cord with pregnancy; one had diabetes insipidus with pregnancy; 9 were not pregnant. After an 8-hour fast 5% glucose in distilled water was given intravenously at a rate of 6 to 8 ml. a minute during the test period. Urine specimens were collected each half hour by catheter until three successive specimens approximately equal in amount were obtained. After the third specimen one arm or foot was immersed in water at 1° C. for 15 minutes. Three more urine specimens were obtained during and after immersion, and blood pressure, respiration rate, and foetal heart rate were recorded at regular intervals. The volume, specific gravity, and chloride content of the urine were estimated. In a quarter of all the patients no changes were noted. In the remainder there was a sharp fall in urine volume per minute during immersion and/or during the succeeding 15 minutes. In nearly all the patients there was a rise in blood pressure. There was no marked difference in the response of toxaemic subjects, but in one pre-eclamptic patient there was anuria for 15 minutes. As urine volume decreased, the specific gravity and chloride content rose. The test was performed on 4 anaesthetized subjects. Although the blood pressure did not rise, urine excretion decreased. [It appears, however, that this was also the case during the pre-immersion period.] In 3 patients with spinal cord interruption no change in blood pressure or in urine volume was observed.

From their data the authors conclude that the blood pressure and urine changes occur through different mechanisms. *G. Loewi*

2553. **The Treatment of Azotaemia by Colonic Water Enemata.** (O wlewaniach wody do jelita grubego w przypadkach azotemii)
M. LANDSBERG. *Polski Tygodnik Lekarski* [*Polsk. Tyg. lek.*] **3**, 1105–1110, Sept. 13–20, 1948. 12 refs.

The author in discussing relevant literature on azotaemia alludes to the fact that in 1924 he (with Gnoinski) introduced peritoneal dialysis in experimental animals and in 1929 (with Szenkier) colonic washouts through an appendicostomy. The latter method has been simplified still further by omitting surgery and reverting to old-fashioned treatment with enemata. Two hours after defaecation or administration of a clearing enema, 1 litre of distilled water is given per rectum twice daily, to be retained for as long as possible; the returned water contained from 17 to 63 mg. of urea per 100 ml. Clinical improvement as shown by cessation of headaches and vomiting and return of appetite was evident in 5 cases after 5 days and in 2 cases after 10 days; in the remaining 3 cases of very advanced uraemia there was no noticeable change. Clinical improvement preceded the lowering of the blood urea level. The improvement is greater than the amounts of urea and other nitrogen compounds washed out would suggest; increased diuresis, usually ensuing on the third day and due to partial absorption of water from the colon, is probably also responsible for improvement. The author does not

recommend the use of greater quantities of water for fear of acute cardiac embarrassment, which occurred in two early cases. In the 7 cases quoted there was advanced chronic uraemia with various complications such as hypertension or cardiac failure. Cure was obviously impossible but marked subjective and objective improvement was achieved, as can be judged by a fall in blood urea level, for example, from 124 to 32 mg. per 100 ml. (case 2) or from 250 to 60 mg. per 100 ml. in 2 months (case 6).

Use of the artificial kidney and peritoneal dialysis are far superior to colonic washouts in removing nitrogen compounds from the organism in cases of azotaemia. The author emphasizes that his method is suitable only for chronic and not too severe cases, the possibility of its repeated and prolonged use and its simplicity of application being the chief factors of value in bringing about slow but marked clinical improvement.

H. Maslowski

2554. **Food Protein Consumption in Glomerulonephritis. Effect on Proteinuria and the Concentration of Serum Protein**

E. C. Persike and T. Addis. *Archives of Internal Medicine* [*Arch. intern. Med.*] **81**, 612–622, May, 1948. 4 figs., 37 refs.

The authors studied the effect of different levels of protein consumption in 2 patients with glomerular nephritis. Both were excreting large quantities of protein; the serum protein concentration was low and both patients were oedematous. Increase in protein intake was followed after a day or two by an increased proteinuria. The patients showed a diurnal variation in proteinuria, the excretion being greater during the day than at night. High-protein diet did not increase the concentration of serum protein, although in one case when protein was reduced to 0·2 g. per kilo body weight the concentration of protein diminished. It is suggested that patients should be given 0·5 g. of protein per kilo body weight plus that amount which they are losing in the urine. Attempts to raise the serum protein level with a high-protein diet result only in an increased protein output.

Alan Kekwick

2555. **The Mechanism of Chronicity and of Progressive Evolution in Nephritis.** (El mecanismo de cronicidad y de la evolucion progresiva de las nefritis)

C. Jiménez Díaz. *Revista Clínica Española* [*Rev. clín. esp.*] **30**, 358–365, Sept. 30, 1948. 3 figs., 18 refs.

Two factors are usually considered responsible for progressive evolution in a case of nephritis: persistence of a focal infection and/or local ischaemia. A direct influence of persistent septic foci on the course of the disease is denied. It is quite possible that persistence of ischaemia after the acute phase would close the following vicious circle: hypertension—renal ischaemia—production of renin—more hypertension, but it is doubtful whether the vascular spasm is the primary cause of ischaemia. It is more likely that the cause is a local swelling of the renal parenchyma within its less elastic capsule—"a true renal glaucoma". This implies a practical consideration. Whenever nephritis with hypertension persists for longer than a month, the author advises decapsulation. A different explanation of pathogenesis is given for those chronic cases of nephritis in which all the symptoms, including hypertension, disappear after the acute stage and in which only albuminuria, persistent or sporadic, marks the progress towards an ultimate sclerosis. In this type—it is claimed—glomerular hyperpermeability is at fault; it is associated with partial re-absorption of proteins in the tubules, where they coagulate and on histological examination present a false picture of lipid degenerative changes. The speed with which this re-absorption leading to sclerosis takes place is regulated by the following factors: (1) the degree of glomerular permeability; (2) the albumin/globulin quotient—the higher the proportion of globulins, the faster the sclerosis progresses; (3) probably the presence of a highly concentrated and acid urine which accelerates the morbid process.

A. Lilker

2556. **Electrophoretic Studies of Plasma and Urinary Proteins in Children with Lipoid Nephrosis**

J. I. Routh, E. L. Knapp, and C. K. Kobayashi. *Journal of Pediatrics* [*J. Pediat.*] **33**, 688–697, Dec., 1948. 5 figs., 14 refs.

Electrophoretic analyses of plasma and urine were carried out in 11 children suffering from nephrosis. Marked changes were found in the percentage composition of plasma proteins, the albumin concentration being much reduced and the concentrations of α and β globulins increased. The more severe the case the greater the reduction in albumin and increase in α and β globulin concentrations. The fibrinogen fraction increased as the albumin fraction decreased. The γ-globulin content proved lower than in normal children. In the urine, α and β globulins were present in every sample, and occasionally γ globulin also. In two cases ascitic and pleural fluids also were examined, the total protein concentration being similar to that of the plasma, though the fluids were lower in β globulin and higher in albumin. Total globulin content was found to be between 3·3 and 4·1 g. per 100 ml. plasma, compared with the normal range of 1·2 to 2·5 g. Total protein averaged 5 g. per 100 ml. plasma, compared with 7·5 g. in thirteen normal children.

These observations confirm the accepted findings that nephrosis results in lowered albumin and raised globulin content of plasma. That α and β globulin are more increased than γ globulin is due to increase in lipoprotein in plasma from patients with nephrosis. The lowered γ-globulin concentration may account for the increased susceptibility of nephrotic children to intercurrent infection. The effect of intravenous administration of concentrated albumin, 25 g. daily, was tried but there was no clinical improvement. Plasma albumin concentration increased temporarily but this was accompanied by increased albuminuria. Diuresis occurred but the oedema rapidly reaccumulated after cessation of the injections.

W. F. Gaisford

Locomotor Disorders

2557. **Studies in Low Backache with Persistent Muscle Spasm**
J. P. PRICE, M. H. CLARE, and F. H. EWERHARDT. *Archives of Physical Medicine* [*Arch. phys. Med.*] **29**, 703–709, Nov., 1948. 2 figs., 2 refs.

Patients with low backache due to such conditions as muscular strain, arthritis, and psychogenic disturbances were studied and compared with the normal. Areas of tenderness in the back were repeatedly mapped out, and the pain was found to vary in intensity and position from day to day and from patient to patient. A series of electromyograms was taken, recording the activity in the muscles of the back during test positions and movements. A wet mixture of modelling clay and plaster-of-Paris was used for the electrodes, which were placed bilaterally over the erector spinae muscles. Patients with backache were found to have patterns of muscular activity differing from the normal. Diagrams are included correlating the position of tenderness with the electromyographic findings. In the acute stage the patients were treated by heat, massage, faradism, and gentle movements. In the chronic stage any residual postural deformity was corrected by relaxation, light exercises, and special rhythmic movements. It was found that patients who achieved good relaxation attained relief from pain.
J. H. Cyriax

2558. **Narrowing of Intervertebral Foramina Resulting from Degenerative Vertebral Processes as a Cause of Neuralgic Pain in the Shoulder and Pelvic Girdle Areas and in the Limbs.** (Die Einengung der Foramina intervertebralia infolge degenerativer Wirbelsäulenprozesse als Ursache von neuralgischen Schmerzzuständen im Bereich des Schulter- und Beckengürtels sowie der Extremitäten)
P. DUUS. *Nervenarzt* [*Nervenarzt*] **19**, 489–503, Nov., 1948. 7 figs., 9 refs.

Degenerative changes in the vertebra and the intervertebral disks have been thoroughly studied by Schmorl and his pupils and described as " osteochondrosis ". That changes of this kind can produce neurological signs and symptoms is not a new finding. The author, however, states that in the German literature too little attention has been paid hitherto to the neurological importance of these changes. He has observed some 50 cases, 6 of which are described in detail; all these patients suffered from " stiff neck ", pain in one or both arms, spreading towards the tips of the fingers, paraesthesiae, and increasing discomfort during the night if the cervical spine was affected; osteochondrosis of the lumbar spine produced lumbago, pains spreading into one or both legs, and increased pain during the night.

In some of these cases no abnormal neurological findings were encountered, in others impairment of reflexes and hypoaesthesia or anaesthesia were found, often on both sides. *X*-ray examination revealed " osteochondrosis ", and oblique radiographs of the cervical or lumbar spine revealed narrowing of the intervertebral foramina. This narrowing of some foramina is, in the author's opinion, the characteristic and important pathological basis of the whole clinical picture, causing compression of the nerves passing through the foramina. None of the patients died, but examination of other necropsy material enabled the author to demonstrate the histological findings in cases of narrowed intervertebral foramina. He promises more findings and facts in a future monograph. As regards treatment, he recommends a plaster-of-Paris jacket and administration of calcium and phosphorus.

[These histological findings are quite interesting, though the patients were very old (83 and 74 respectively) and obviously suffering from very advanced " osteochondrosis ". Some of the author's statements are unacceptable, for instance, that disk herniation plays no part in the pathology of the cervical spine, that the L5 dermatome is situated at the lateral side of the foot, and that the reflex arc of the ankle-jerk involves L5 and S1, 2, and 3.] *F. K. Kessel*

2559. **Studies on the Agglutinins Against Hemolytic Streptococci in Rheumatic Diseases.** [In English]
S. WINBLAD and G. EDSTRÖM. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 715–727, 1948. 4 figs., 22 refs.

The authors review previous work on the agglutination of streptococci by sera from patients with rheumatic fever and rheumatoid arthritis. They point out that there are two types of agglutination; in one type the antigen appears in non-encapsulated living streptococci and disappears after the organisms have grown for more than 14 hours, or after shaking and centrifugation, this being termed " L agglutination "; in the other an antigen occurs in autoclaved haemolytic streptococci and is termed by Thulin " O-antigen ".

The authors report a study of L agglutination of Group A type I haemolytic streptococci suspended in a special broth (formula given) in a series of 206 sera from cases of rheumatoid arthritis (nearly all cases being tested repeatedly), a control series of 105 normal sera, and 72 sera from cases of rheumatic fever. The inactivated serum, serially diluted with 0·3% NaCl to titres up to 1 in 640 is incubated for 2 hours at 52° C. after addition of an equal broth suspension, and the result read after leaving overnight in the refrigerator. Three degrees of positive agglutination are recognized, particle and clump formation being considered positive. Positive agglutination (beyond a titre of 1 in 10) developed in 68% of sera from cases of rheumatoid arthritis compared with 6%

of the control sera, and there was a significant correlation with the rate of erythrocyte sedimentation. In rheumatic fever, 35% of sera gave a positive agglutination: 5 individual charts are shown. It appears that the agglutination titre becomes raised only several months after the acute stage (22% were positive up to 4 months, whereas 47% of the sera were positive after 4 months from the onset). Three explanations of these findings are suggested: (1) The late positive reaction results from a continuing streptococcal infection. (2) The streptococcus may change after a period and produce this different late antigen (the most feasible explanation according to the author). (3) The reaction is a non-specific flocculation reaction such as is seen with collodion particles (Wallis). *E. G. L. Bywaters*

2560. **Effect of Blood Transfusion on Rheumatoid Arthritis**
N. R. W. SIMPSON and D. H. BROOKS. *Proceedings of the Royal Society of Medicine* [*Proc. R. Soc. Med.*] **41**, 609–613, Sept., 1948. 8 figs., 7 refs.

Blood transfusion as a method of treatment in rheumatoid arthritis was first used in 1931 in Britain and before the introduction of gold salts was considered by many authorities to be the most promising line of treatment, apart from general measures. The aim of the present investigation was to determine the effect of transfusions of whole blood, concentrated red cells, and plasma on both the blood picture and the general condition of the patients. The results of plasma protein estimations in 24 cases, both before and after transfusion, and in 5 cases of ankylosing spondylitis are analysed. The authors do not wish to draw any conclusions from this small series of cases, and it is their intention to continue these studies with adequate normal controls. They did note, however, that in those cases in which the plasma protein values returned to normal there was a coincident improvement in the general condition of the patient.

W. S. C. Copeman

2561. **Metastatic Calcification. Is the Role of Hypercalcemia Over-emphasized as a Toxic Manifestation of Vitamin D Therapy in Rheumatoid Arthritis?**
A. COHEN, J. G. REINHOLD, and R. COHN. *Industrial Medicine* [*Industr. Med.*] **17**, 442–446, Nov., 1948. 1 fig.

In the United States many reports have been published on toxic manifestations of intensive vitamin D therapy for rheumatoid arthritis. The authors review the literature of metastatic calcification in great detail and quote Mulligan who found that the major causes of such calcification are bone disease, chronic renal disease, hyperparathyroid states, and hypervitaminosis D. Many theories have been formulated to account for the more obscure forms of metastatic calcification. Barr found that acid diets with a high calcium and phosphorus content led to diffuse calcification in rats, but similar alkaline diets did not do this. The authors suggest that for calcification to take place there must exist certain changes in the blood chemistry and certain localized tissue changes. While vitamin D, when given in large amounts, raises the serum calcium level this is not in itself necessarily harmful. The reason why certain patients develop metastatic calcification remains obscure. It may be that a change in calcium ionization occurs in the blood.

The authors give details of serum calcium levels found in 47 of 150 patients suffering from rheumatoid arthritis and treated with large doses of vitamin D. While serum calcium levels of from 12 to 16 mg. per 100 ml. were common, no metastatic calcification occurred in any patient although treatment went on for as long as 30 months. In three patients there was a temporary increase in the blood urea level. The authors conclude that a high serum calcium level alone does not lead to metastatic calcification and that there must be local changes in the tissues. If the serum phosphorus concentration is increased there is a greater tendency to calcification. Normally the taking of a meal results in a lowering of the plasma phosphate level. The authors found that in rheumatoid arthritis treated by vitamin D there is a progressive fall in postprandial phosphate concentration for about 8 months, but after this period the concentration is progressively less affected by the taking of a meal. Thus during the first months of treatment there is a lessened danger of calcification.

The authors found that in most cases in which calcification had been reported other factors had been present which increased the potency of vitamin D or aggravated its effects. They also suggest that in arthritis metastatic calcification commonly occurs in the absence of vitamin D therapy and that this calcification cannot always be attributed to the vitamin. It is possible, however, that in arthritic patients there is a greater susceptibility to factors causing calcification. Immobilization, prolonged debilitation, milk diet, vomiting, and starvation are all suggested as possible factors favouring calcification in arthritics. Renal injury may result from vitamin D intoxication but is not necessarily due to this cause. It is always wise to investigate the renal condition before using this form of treatment.

It is suggested that vitamin D may possibly exert some of its effects through the interaction of calcium in high concentration with the respiratory enzymes in tissue cells such as the kidney tubules. Similarly, if phosphate levels in the blood are high, a high concentration of calcium may lead to deposition of calcium in the tissues. The authors conclude that the risks of intensive vitamin D therapy are not as great as they are generally believed to be. They advocate the careful selection of patients who are to receive vitamin D in order that those in whom contraindications exist should not be treated with it. They also advocate a careful watch for early signs of toxic manifestations. They suggest that prolonging vitamin D therapy beyond one year may be inadvisable.

W. Tegner

2562. **Anaemia Problems in Rheumatoid Arthritis.** [In English]
F. NILSSON. *Acta Medica Scandinavica* [*Acta med. scand.*] Suppl. 210, 1–193, 1948. 7 figs., bibliography.

Neurology

2563. **Experimental Hormonal Changes in the Cerebral Circulation.** (Modifications hormonales expérimentales de la circulation cérébrale)
H. BARUK, —. DAVID, —. RACINE, and —. VALLANCIEN. *Revue Neurologique* [*Rev. neurol.*] **80**, 497–516, July–Aug., 1948. 7 figs., 28 refs.

The first part of this paper consists of a report of animal experiments on the influence of certain hormones on the cerebral circulation. All the substances used were applied directly to exposed cortex and each was injected intravenously. Folliculin—that is, follicle stimulating hormone—produced slight vasodilatation when given intravenously. Testosterone caused slight dilatation of the vessels in male animals. Acetylcholine resulted in extensive dilatation of the cerebral vessels and acute gross oedema of the brain; if larger doses were given the animals died. Injection of an anterior pituitary hormone preparation (prolan) produced a cataleptic condition, called by the authors "hypophysial catalepsy", after an initial constriction of the cerebral vessels.

In the second part of the paper the authors analyse their results and discuss the hormonal treatment of psychoses. *F. K. Kessel*

2564. **The Normal Haemolysin Content of the Cerebrospinal Fluid in Multiple Sclerosis and in Other Diseases of the Nervous System.** (A liquor normál haemolysin tartalma sclerosis polyinsularisnál és más idegrendszeri megbetegedéseknél)
L. KÖNYVES-KOLONICS and I. HUSZÁK. *Orvosi Hetilap* [*Orv. Hetil.*] **89**, 471–474, Oct. 24, 1948. 6 refs.

The unstable colloidal systems of the nervous tissue are very sensitive to physico-chemical changes in the surrounding tissues. In the central nervous system the nervous tissue is protected by membranes which participate actively in the selection of substances necessary for the brain and the elimination of pathological products. The biological behaviour of these membranes can be examined by investigating their permeability, particularly to components of the circulating blood to which the membranes are not permeable under normal circumstances, such as enzymes, immune bodies, and certain inorganic ions. Of these compounds the authors, at the Psychiatric Clinic of the University of Budapest, chose the normal haemolysins of the blood which appear in the cerebrospinal fluid only under pathological conditions. They examined the blood–cerebrospinal-fluid barrier in different organic lesions of the central nervous system and also in normal persons and compared conditions with those in patients suffering from disseminated sclerosis. Human serum always contains a small amount of haemolysin, capable of lysing sheep red cells in presence of complement, but this so-called normal haemolysin can pass into the cerebrospinal fluid only if the permeability of this barrier is pathologically increased. The first phase of the reaction is examined after 0·5 ml. of sheep cells (5% solution) is added to 5 ml. of cerebrospinal fluid, the mixture kept for 2 hours at 37° C. and centrifuged, and the reaction read; if it is negative titrated guinea-pig complement is added, the mixture kept for another 3 hours at 37° C., and the reaction read after centrifugation. In a normal case no lysis is observed. In 21 cases of disseminated sclerosis positive reactions were found in 16, of which 6 were in the first and 10 in the second phase. The reaction was positive in the acute phases of the disease and had no connexion with any other pathological findings in the cerebrospinal fluid but only with the activity of the disease. This increased permeability was not found in any other disease, apart from meningitis, general paresis of the insane, and polyneuroradiculitis. *E. Forrai*

2565. **Winking-jaw Phenomenon**
R. WARTENBERG. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 734–753, June, 1948. Bibliography.

In a clinical, physiological, and phylogenetical study of the winking-jaw phenomenon (first described in 1902 by von Sölder as the "corneo-mandibular reflex") the author regards it as an inverted and reversed Marcus Gunn (jaw-winking) phenomenon. It is an associated movement between the orbicularis oculi and the external pterygoid muscle which formerly belonged together, became separated in the course of development, and are reunited in action as a release phenomenon due to a supranuclear lesion. It is therefore to be regarded as a valuable diagnostic test for supranuclear lesions of the trigeminal nerve. The various forms of pathological associated movements of the ocular muscles are reviewed and classified. *W. H. McMenemey*

2566. **Studies on Sweat Secretion in Man. I. Innervation of the Sweat Glands of the Upper Extremity; Newer Methods of Studying Sweating**
M. G. NETSKY. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **60**, 279–287, Sept., 1948. 5 figs., 20 refs.

This is a study of sweating in the hands after a Smithwick type of preganglionic sympathectomy in 15 patients. Two special methods of demonstrating sweat secretion were used, which were considered to be more accurate than the starch-and-iodine and "chinizarin" techniques or the skin-resistance method. In the tannic-acid procedure (Silverman, and Powell, *Amer. J. med. Sci.*, 1944, **208**, 297) the area to be tested is painted with tincture of ferric chloride and then placed for 3 minutes on paper impregnated with tannic acid. When

sweating occurs the iron salt is dissolved out and the resulting formation of ferric tannate leaves an ink-spot on the paper. In this way a permanent record of the distribution of the sweating glands is obtained without photography. The prism method is a new one. The part to be tested is pressed against one side of a prism and a light is thrown into the second side, the appearances being observed through the third. In a normal thumb a bright and shiny print is seen; in the thumb on the sympathectomized side the print is dull and hazy, and scattered on the ridges where the sweat glands are located small bright points are seen, due to moisture from the sweat glands.

In the 15 patients who had undergone sympathectomy, instead of the expected complete anhidrosis, a small number of functioning glands were found scattered throughout the sympathectomized area; in the fingertips there were reckoned to be 2% of the total number of glands. Activity was seen as soon as 2 days after operation, making regeneration of fibres an unlikely explanation. From the nature of the Smithwick preganglionic operation the author concludes that the sweat glands which remain active are probably innervated by the grey ramus of the first thoracic root, which previously has not been thought to play any part in the sympathetic innervation of the upper extremity in man.

J. W. Aldren Turner

2567. **Referred Pain and Associated Phenomena**
D. C. SINCLAIR, G. WEDDELL, and W. H. FEINDEL. *Brain* [*Brain*] **71**, 184–211, 1948. 5 figs., bibliography.

The authors review the literature and conclude that there are two " opposing views " concerning the phenomenon of referred pain. The first is that some mechanism located centrally is responsible; the other that the phenomena are produced by events at the periphery. They conclude that neither hypothesis explains all the observed facts. They then review the experimental work and expound a theory dependent on the existence of axon branching. In view of the frequent existence of axon branching in other mammals, the supposition that this particular arrangement might also occur in man is not unwarranted.

Arguing from the experimental production of referred pain by saline injection near the dorsal nerve trunks lying near the interspinous ligaments, the authors suggest that impulses arising in the territory of the posterior division and in the anterior division must occasionally find themselves in joint possession of a single "final " pathway to the pain-receiving centre. If it be assumed that the centre is incapable of distinguishing the ultimate source of the impulses reaching it by these common pathways it becomes possible to explain how stimulation of one branch of such an axon might give rise to the sensation of referred pain in the district served by the other branch. It may be assumed that such bifurcating axons are relatively infrequent, which could explain why referred pain seldom arises from stimulation of the skin or deep tissues whereas it does from stimulation of a nerve trunk. If the sister branches are scattered at random within the territory then they are probably isolated from each other, which would explain the imperfect localization and unpleasant character of referred pain. The production of cutaneous hyperalgesia is explained by the liberation of a metabolite at the nerve endings as a result of antidromic impulses passing down the cutaneous limbs of the branched axon systems. It is further suggested that the other branch of the axon may terminate not in the skin but in deep tissues, so giving rise to phenomena of referred deep tenderness. Anaesthetizing the area of reference will abolish the metabolic element but leave unchanged the element of central misinterpretation.

By suggesting that branched axons exist, having one limb supplying a viscus and the other skin or deep somatic tissue, the authors expand their theory to cover referred pain from visceral structures. They even suggest tentatively that a reference by stages may be possible; the branched axon from a viscus causes appearance of a metabolite in a muscle which, by affecting a second branched axon, might lead to the production of a similar disturbance in an area of skin. *N. S. Alcock*

CENTRAL NERVOUS SYSTEM

2568. **Phosphorus Metabolism in Disseminated Sclerosis**
A. WEIL and G. B. BRADBURNE. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] **7**, 447–452, Oct., 1948. 16 refs.

In view of a theory that disturbance of phospholipid metabolism might cause the breakdown of myelin in disseminated sclerosis, studies of phosphorus metabolism were made. Intake and output of phosphorus were estimated for 5 days after stabilization on a low-phosphorus and a high-phosphorus diet, and it was found that, while in controls there was a negative balance or stabilization, there was a positive balance in disseminated sclerosis with marked retention on the high-phosphorus diet. Sufferers from disseminated sclerosis have a poor appetite, especially for butter, eggs, and milk, which suggests an intuitive regulation of phosphorus intake. The phosphorus retention may be due to active metabolism of phospholipids in the brain, to elimination from the brain, to retention of phosphorus in other tissues (as glia), or to reduced demands from muscular weakness.

Gwenvron M. Griffiths

2569. **A Chemical Analysis of the Phospholipids of the Brain in Disseminated Sclerosis**
A. WEIL. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] **7**, 453–456, Oct., 1948. 6 refs.

Chemical analysis of unfixed brains from cases of disseminated sclerosis revealed an acetone extract (cholesterol, fats, and fatty acids) lower in amount than normal in grey matter but normal in white matter, with low phosphorus content. The alcoholic fraction (containing phospholipids) was quantitatively normal, but that from the grey matter contained only half the normal amount of phosphorus and that from the white matter two-thirds the normal amount. The residue was again quantitatively normal, but its phosphorus content was increased

by 25% as regards the grey matter and by 50% as regards the white matter. It is suggested that the glia retains the excess of phosphorus, as a similar increase was found in the brain in cases of arteriosclerosis and vascular syphilis.

Gwenvron M.Griffiths

2570. **Intramuscular Use of Tubocurarine in Chronic Spasticity due to Disease of Central Nervous System. Further Clinical Investigation**

M. NATHANSON, S. LESSER, G. GORDON, and N. GRESSER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **60**, 77–80, July, 1948. 2 refs.

A preparation of *d*-tubocurarine chloride in peanut oil and white wax, given under the conditions described, affords no improvement in active motion, passive motion, or functional use in chronic spastic diseases due to involvement of the central nervous system. Extrapyramidal diseases also seem not to be affected by this preparation of curare. The toxic side reactions are minimal. [Authors' conclusion.]

2571. **Idiocy, Epilepsy, Bilateral Athetosis and a Medullary Syndrome as Late Sequelae of Nuclear Jaundice.** (Idiotie, épilepsie, choréoathetose double avec un syndrome médullaire, séquelles tardives de l'ictère nucléaire)

A. DECHAMPS and L. VAN BOGAERT. *Acta Neurologica et Psychiatrica Belgica* [*Acta neurol. psychiat. belg.*] **48**, 480–492, Oct., 1948. 5 figs., 8 refs.

The authors report a case (with necropsy findings) of idiocy, epilepsy, and bilateral choreo-athetosis and spinal cord symptoms in a male born with icterus gravis. Mental deterioration set in at the age of 2, fits at 5, and involuntary movements at 26. The symptoms progressed steadily till the patient's death in a state of complete dementia at the age of 48. Necropsy revealed in the subcortical white matter of both hemispheres numerous areas which had the appearance of vascular lesions, although no corresponding changes in the blood vessels were seen. There was much degeneration with gliosis of the globus pallidus and corpus of Luys with sparing of the putamen. The spinal cord showed sclerosis of the posterior columns and atrophy of the anterior grey horns.

J. St. C. Elkington

2572. **Role of Afferent Impulses in Experimental Convulsions**

E. GELLHORN and H. M. BALLIN. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 718–733, June, 1948. 10 figs., 15 refs.

Experiments were made on over 40 cats under " dial " anaesthesia to ascertain the influence of afferent impulses on convulsive movements and on cortical and hypothalamic potentials. The cortical areas studied were the motor, sensory projection, and suppressor, the potentials being recorded through a four channel Offner crystograph. Condenser discharges were supplied at a rate of 90 per second. The effect of afferent impulses elicited by stimulation either of the sciatic nerve (ligation proved to be the most effective procedure) or of the hypothalamus was studied after intravenous injection of doses of picrotoxin; it was found that either method induced convulsions for varying periods during the act of stimulation or after; if the convulsions existed before stimulation, the afferent stimuli might greatly aggravate the convulsions. The cortical potentials invariably increased both in amplitude and frequency and the observation could be repeated several times on the same animal although the level of picrotoxin poisoning at which this phenomenon occurred varied widely in different animals in spite of uniformity in the technique of anaesthesia. Severe discharge, of an intensity to warrant convulsions, could be precipitated in motor areas of the cortex as a result of afferent stimuli yet without overt convulsive movements. Sometimes a lack of parallelism was noted between the hypothalamic and cortical potentials, the data suggesting that, although the hypothalamus may initiate convulsions, it is not responsible for maintaining the activity nor does it, under the conditions of the experiment, control the rate and intensity. The observation that stimulation of the hypothalamus may evoke or aggravate convulsions suggests that emotional processes have a similar effect. It appeared to be a fact that cortical regions which are in a state of higher excitability than others react to afferent stimulation with an intensification of convulsive discharges, whereas areas of lesser excitability show the opposite effect. Observations suggested in fact that afferent impulses may have a dual effect on overt convulsions, decreasing or increasing them according to the intensity of stimulation. Other conditions being equal, decrease is due to strong, and increase to weak, stimuli. Intensification of " convulsive " potential seems to be associated with increased recruitment and decreased synchronization, whereas suppression of convulsive potentials is accompanied by decreased synchronization only.

W. H. McMenemey

2573. **Survival of Patients with Cerebral Haemorrhage Dying in Hospital**

W. MCI. ROSE. *Lancet* [*Lancet*] **2**, 561–563, Oct. 9, 1948. 6 refs.

Clinical and necropsy records of 205 unselected cases of cerebral and cerebellar haemorrhage, including intracranial aneurysm, in patients dying in hospital, were studied to determine the average duration of life after the onset of symptoms. The term primary was used for haemorrhages with no antecedent thrombosis, while those which followed cerebral thrombosis after a period of a week or more were called secondary. No significant differences of survival times were found for different sites within the cerebral hemispheres. Of the 65 patients with primary haemorrhage none survived longer than 4 days; in the secondary group of 27 cases no death occurred before the seventh day after cerebral thrombosis. Cardiac hypertrophy, probably in association with hypertension, appeared to be an important factor in the rupture of intracranial aneurysm but not in the ordinary type of spontaneous cerebral haemorrhage. Rather more than 80% of the patients with primary haemorrhage died within 24 hours of the onset. Haemorrhage into the brain stem and massive

rupture of an intracranial aneurysm were associated with the shortest survival period; the longest survival time was noted in cases of haemorrhage into the cerebellum. The shortest interval before death occurred was 2 hours, a finding which justifies the view that cerebral haemorrhage is rarely a cause of sudden death.

R. M. Stewart

2574. **Dilatations and Elongations of the Internal Carotid Artery. Functional and Organic States.** (Les dilatations et allongements de l'artère carotide interne. États fonctionnels et organiques)

J. N. TAPTAS. *Revue Neurologique* [*Rev. neurol.*] **80**, 338–354, May, 1948. 12 figs., 23 refs.

The author presents records of 7 cases of diffuse dilatation and elongation of the internal carotid artery, associated with different varieties of cephalic and facial pain and in some cases cranial nerve palsies and contralateral hemiparesis. The author considers that these cases may be congenital or senile in origin, or be brought about by vasomotor imbalance.

J. St. C. Elkington

2575. **"Tumour" Symptomatology of Voluminous Aneurysms of the Vertebral and Basilar Arteries.** (La symptomatologie tumorale des volumineux anévrysmes des artères vertébrales et basilaires)

T. ALAJOUANINE, J. LE BEAU, and R. HOUDART. *Revue Neurologique* [*Rev. neurol.*] **80**, 321–337, May, 1948. 1 fig., 14 refs.

The authors report 2 cases of large saccular aneurysms of the vertebral and basilar arteries in which symptoms and signs were so similar as to seem to form a basis for the diagnosis of similar cases in the future. In each case there was a picture of headache, dysphagia and other signs of a partial paralysis of the lower cranial nerves, and a contralateral hemiparesis, all of which had developed in the course of 1 to 2 years. In each case the posterior fossa was opened surgically without establishing the nature of the lesion. Death occurred shortly afterwards. In each case necropsy revealed a large saccular aneurysm formed by the vertebral and basilar arteries and deeply embedded in the anterior aspect of the pons. The authors refer to similar cases in the literature and discuss the aetiology and symptomatology of the condition. The latter includes headache, bulbar palsy, often asymmetrical, and contralateral hemiparesis. Sensation is notably normal. *J. St. C. Elkington*

2576. **Studies on Acute Disseminated Encephalomyelitis Produced Experimentally in Rhesus Monkeys**

E. A. KABAT, A. WOLF, and A. E. BEZER. *Journal of Experimental Medicine* [*J. exp. Med.*] **88**, 417–426, Oct., 1948. 1 fig., 15 refs.

As a result of further experiments, another study is presented on acute disseminated encephalomyelitis in monkeys produced by injection of brain tissue with paraffin and killed tubercle bacilli as adjuvants. In the present work the effect of injection of various types of brain tissue was considered and also the stability of the antigen in the injected brain tissue. Emulsions of chicken, monkey, and human brain when treated with adjuvants all produced the disease, but frog and fish brain gave negative results. Negative results were also obtained from plain emulsions of monkey and human brain without adjuvants, from emulsions of these brains with "aquaphor" and paraffin but without tubercle bacilli, and from an emulsion of aquaphor, paraffin, and tubercle bacilli without brain tissue. Previous experiments had shown that the encephalitis-producing antigen was absent from the foetal rabbit. The authors therefore investigated the results of injecting with the usual adjuvants brain emulsions from rabbits of varying ages. They found that the antigen did not appear in the brain until the rabbits were 12 days old, whereas injection of the spinal cord emulsion of a 3-day-old rabbit caused encephalomyelitis in 3 monkeys out of 4. Attempts to produce the disease by injection of the serum of monkeys with the disease, and of the serum of rabbits immunized with monkey brain tissue containing adjuvants, were unsuccessful, as were also injections of passive peritoneal exudates obtained in monkeys suffering from encephalomyelitis by intraperitoneal injection of paraffin oil. Injection of extracts of spleen and lymphoid tissue from affected monkeys also gave negative results. The capacity of the antigen in brain tissue to produce encephalomyelitis was not much lowered by heat, fixation in formalin, or exposure to ultrasonic vibration. Alcohol or acetone extraction, however, completely destroyed this property, both the extract and the residue being inactive.

[The authors are to be congratulated on the scope of their experiments and the succinct presentation of their results.] *Ruby O. Stern*

2577. **Meningo-neurobrucellosis.** (Sulle meningo-neurobrucellosi)

P. SARTESCHI. *Rassegna di Studi Psichiatrici* [*Rass. Studi psichiat.*] **37**, 555–575, Sept.-Dec., 1948. 22 refs.

Eight cases of meningo-neurobrucellosis are described. In 4 cases only the meninges appeared to be affected; in the other 4 either the brain or the spinal cord was also involved. The author states that in these cases a definite and characteristic "liquor syndrome" exists—namely, xanthochromia, reduction of the glucose content, and presence of a fibrin clot in the shape of a cone.

F. K. Kessel

2578. **Results of Streptomycin Treatment of 19 Patients with *H. influenzae* Meningitis; Comparison with Earlier Results.** (Uitkomsten van de streptomycinebehandeling bij 19 lijders aan influenza-meningitis, vergeleken met vroegere uitkomsten)

W. J. BRUINS SLOT, L. A. HULST, and H. W. STENVERS. *Nederlandsch Tijdschrift voor Geneeskunde* [*Ned. Tijdschr. Geneesk.*] **92**, 2973–2983, Sept. 25, 1948. 22 refs.

A comparison is made of the results of treatment by different (Netherlands) physicians of two groups of cases of *H. influenzae* meningitis, one (32 patients, including 21

under 2 years of age) with drugs other than streptomycin, and the other (19 patients, comprising 17 children under 2 years, a child of 4, and one adult) receiving streptomycin with or without other drugs. Of the first group 4 recovered and of the second group 14. Of the fatal cases in the second group 2 ran a fulminating course with death within 3 days; in one case necropsy revealed a subdural abscess; one patient had been ill for 27 days before treatment started, and the fifth bacteriological examination showed a *Listeria* to be present as well.

K. Kraaijenbrink (*Excerpta Medica*)

2579. **Gliomas of the Cerebellopontine Angle**

J. W. KERNOHAN, H. W. WOLTMAN, and A. W. ADSON. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] **7**, 349–367, Oct., 1948. 14 figs., 5 refs.

The authors report a series of 10 cases of gliomata of the cerebello-pontine angle, 8 of the tumours being ependymomata and 2 fibrous astrocytomata. Seven of the cases were in children, which may be of assistance in distinguishing these tumours from the much commoner lateral recess neoplasms—namely, acoustic neurofibromata and dural meningiomata. Seven of the 10 cases were in females. *J. St. C. Elkington*

PERIPHERAL NERVES

2580. **Trigeminal Neuralgia Treated with Cuprelone**

A. M. G. CAMPBELL. *Lancet* [*Lancet*] **2**, 690–691, Oct. 30, 1948. 4 figs.

"Cuprelone" is cuproallyl-thiourea-sodium benzoate and contains 19% of copper; it is obtainable in dry ampoules containing 10 to 100 mg., and for intravenous injection the powder is dissolved in sterile distilled water. Copper is useful in preventing swayback in sheep, but is ineffective in disseminated sclerosis. In a patient suffering from disseminated sclerosis, and who also had severe trigeminal pain, it was noticed that the pain was alleviated immediately after an injection of cuprelone. Four patients with trigeminal pain were treated with the drug and all obtained some relief. In a number of instances single injections of 50 or 100 mg. seemed enough; in others more distinct relief followed a course of injections of 800 mg. in 6 weeks. The drug was given to 9 further patients, 6 of whom obtained relief. The question is raised whether the drug exerts a specific effect on the trigeminal nerve nucleus as do triethylene and stilbamidine. *Geoffrey McComas*

2581. **BAL Therapy of Severe Peripheral Neuropathies**

A. R. FURMANSKI. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **60**, 270–278, Sept., 1948. 13 refs.

Four cases of severe peripheral neuropathy of metabolic or infective origin were treated with 2 : 3-dimercaptopropanol (BAL) in doses of 1·5 to 3 mg. per kilo of body weight by daily injection for periods of 9 to 22 days. BAL has been proved to be of value in intoxication with various heavy metals, and in certain circumstances "has the ability to restore disrupted cellular metabolism by its action on enzyme systems". The author considered that the basic cause of the peripheral neuropathies was a reversible biochemical disorder of the neurones without structural damage, and that BAL might restore enzymatic equilibrium. The 4 patients treated had not shown any improvement on large doses of crude liver extract and vitamins. Three improved rapidly after treatment with BAL was started, and there was gradual improvement in the fourth case.

J. W. Aldren Turner

See also Section Locomotor Disorders, Abstract 2558.

OTHER NERVOUS DISEASES

2582. **Activation of Seizures and Electroencephalographic Disturbances in Epileptic and in Control Subjects with "Metrazol"**

C. CURE, T. RASMUSSEN, and H. JASPER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 691–717, June, 1948. 6 figs., 32 refs.

In view of conflicting reports on "metrazol" (pentamethylenetetrazol) the authors, working at Montreal, set out to assess the value of the drug for inducing electroencephalographic changes, as a diagnostic measure, in subjects believed to be epileptic. They studied 132 patients and 42 controls and found that the most reliable form of administration was by slow intravenous injection, the advantage of this method being the gradual building up of the drug in the brain with the result that a predisposed area became activated before epileptic discharge became generalized.

Epileptiform discharge was increased or induced in the electroencephalogram in 80% of the known epileptics, a clinical response which revealed the nature of the onset of the spontaneous attacks occurring in 56% of them. The author emphasizes that only the induction of definite epileptiform patterns should be accepted as diagnostic of epilepsy, for paroxysmal disturbances of various kinds occurred in 26% of the control subjects. In 1 out of 29 control subjects who received the maximum dosage of 400 mg. an epileptiform seizure was induced, being preceded by the appearance of paroxysmal bifrontal high-voltage rhythmic waves with a frequency of 4 or 5 a second and increased by ventilation. Susceptibility to metrazol was maximal in patients with idiopathic epilepsy, especially with a bilaterally synchronous wave and spike pattern, and less in those with superficial focal epileptogenic lesions of the cortex. It was less in patients over the age of 40, in epileptics with infrequent seizures, and in those receiving anticonvulsant treatment, so that susceptibility seemed to be related to the patient's convulsive threshold. Occasionally, on the other hand, epileptics were met with who were resistant to large doses of the drug (in one instance 800 mg.).

Focal epileptogenic lesions, which had been induced in 7 monkeys (*Macaca mulatta*) for another series of investigations by means of the alumina cream technique, were activated after the intramuscular administration of

metrazol. Within 5 minutes the pre-existing localized spike discharge increased and in 5 animals this was followed by a convulsive seizure of Jacksonian onset almost identical with that of the spontaneous attacks. In 3 the attacks progressed to a seizure which was more severely generalized than those usually observed in the spontaneous attacks. In 2 animals with experimental lesions metrazol induced attacks before they were due to occur spontaneously.

The authors believe that, when used in conjunction with the electroencephalogram, the slow intravenous injection of metrazol in a 2% solution at the rate of 20 mg. per half minute up to a maximum of 400 mg. has definite advantages over other methods at present in use for the purpose of obtaining a clear diagnosis in cases in which the nature of seizures is obscure.

W. H. McMenemey

2583. **Therapeutic Action in Epilepsy of Drugs Inhibiting the Sympathetic and Parasympathetic Nervous Systems.** (Sull'azione terapeutica negli epilettici di farmaci inibenti l'orto e il parasimpatico)
G. PADOVANI. *Rassegna di Studi Psichiatrici* [*Rass. Studi psichiat.*] **37**, 607–616, Sept.–Dec., 1948. 13 refs.

The author treated 32 patients suffering from genuine epilepsy according to the method of Bulsi—namely, intramuscular injections of " bellafoline " and " gynergen " (ergotamine tartrate) in rather large doses. Of these patients 23 received the drugs for one month only; 55% " positive " results were achieved in this group. Nine patients were similarly treated, but were given anticonvulsive drugs in addition; in 78% of these cases " the therapeutic effect was augmented ". Favourable responses, the author states, are decrease in the number of fits: this often persisted some time after the treatment of Bolsi had been finished; and general improvement in the mental attitude and behaviour of the patient. The author is so satisfied with his results that he recommends the treatment in every severe case of idiopathic epilepsy; he believes that by " sedation of the autonomic nervous system with bellafoline (parasympathetic) and ergotamine (sympathetic) " a differentiation of the various physiopathological types of epilepsy may be possible.

F. K. Kessel

2584. **The Pathogenesis of the Epileptic Attack, in the Light of some Data Derived from Experimental Electroshock.** (La patogenesi dell'accesso convulsivo epilettico, alla luce di alcuni dati sperimentali da elettroshock)
F. GRANONE. *Rivista di Neurologia* [*Riv. Neurol.*] **18**, 308–336, May–June, 1948. 7 refs.

The theories of the pathogenesis of the epileptic attack are reviewed. The author supports the theory which assumes that the tonic and clonic phases are due to the discharge of the extrapyramidal and pyramidal systems respectively. In the presence of a lesion of either system the convulsion should therefore be modified. Twenty-five patients suffering from diseases such as severe Parkinsonism with unilateral and bilateral involvement, hemiplegia, athetosis, and choreo-athetosis were subjected to electric shocks. Due care was taken to use threshold doses, for if the convulsion was too severe it failed to reveal the variations and asymmetries of the type of attack. None of the patients suffered any inconvenience or ill effects during the treatment. With three exceptions, a modification of the tonic or the clonic phase was noted in every case. From his observation the author concludes that the tonic phase is the expression of the involvement of the extrapyramidal system whilst the clonic phase represents the pyramidal component of the fit. The results cannot be considered entirely conclusive until it is shown that lesions of the extrapyramidal cortex or of the subcortical convulsant centres can cause the same modification of the fit in response to electric shock. Diagnosis, technique, and results are given in detail for each case.

A. Limentani

2585. **On the Neuromuscular Transmission in Normal and Myasthenic Subjects.** [In English]
F. BUCHTHAL and L. ENGBAEK. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] **23**, 3–11, 1948. 13 refs.

Transmission at the myo-neural junction was studied by the intra-arterial injection of acetylcholine. Acetylcholine hydrochloride diluted in normal saline to a volume of 2 ml. was rapidly injected after arterial occlusion into the brachial artery. In 23 normal subjects localized flexion of the fingers with flushing and sweating was produced by a dose of 200 to 300 μg. In women the threshold was slightly lower (150 to 250 μg.). In 2 cases of amyotrophic lateral sclerosis the threshold dose was below 125μg. and in 2 cases of muscular dystrophy the threshold was raised to 450 to 550 μg. Of 7 myasthenic subjects (6 females) investigated 6 had a raised threshold (400 to 800 μg.), and in one patient upon whom a thymectomy had been performed the figure was normal. Five of the patients were then given neostigmine (0·5 mg. intramuscularly) and in 3 of them the threshold for acetylcholine was reduced. In 2 of the 3 patients this lowered threshold was maintained with di*iso*propylfluorophosphonate (D.F.P.). One case in which the threshold had not been lowered by neostigmine also failed to improve with D.F.P.

The semitendinosus muscle of the frog was suspended in serum taken with venous occlusion after exercise of the forearm in 4 cases of myasthenia gravis, but the curare-like action described by Wilson and Stoner was not demonstrable.

In addition 3 patients were given D.F.P. intramuscularly in a 0·2% solution in oil in doses of 0·5 to 2·4 mg. daily. Two patients were able to stop taking neostigmine and in the third the dosage could be reduced. Thus, while intra-arterial acetylcholine in large doses (20 to 40 mg.) causes paresis, small amounts produce a transient motor response in normals. Myasthenic subjects, however, require more, possibly because of the presence of a curare-like substance, but such a substance was not demonstrable in these experiments.

Fergus R. Ferguson

Psychiatry

2586. **Experiments in the Improvement of Reading in a Group of Educationally Subnormal Boys**
H. C. GUNZBURG. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 809–833, Oct., 1948. 1 fig., 8 refs.

Three forms of exercise are described: a " syllabication drill " to improve fluency and accuracy in word production; " comprehension " exercises, which included training in logical thinking and attention to detail and of extension of vocabulary; and " comprehension card " exercises to improve speed and efficiency of comprehension. The pupils were educationally backward boys with an I.Q. between 92 and 55 in a senior class of a residential special school. Evidence is cited in corroboration of the author's opinion that the exercises were effective.

Maladjustment was thought to be a more important cause of inferiority than intellectual deficiency, and certain features of the exercises were designed to overcome the discouragement resulting from previous failure. Thus the " syllabication " drill, an entirely new method to the children, was unaffected by previous prejudices and gave them a feeling of achievement and satisfaction with every word mastered. It combined elements of the phonetic and sight-reading methods and made use of both nonsense and meaningful words, split up into syllables and made up according to certain phonetic rules. The children were taught to pronounce these words, most of which were long. After 6 months of the drill the Burt test revealed that the level of mechanical reading had been raised by an average of 1 year and 8 months.

In the " comprehension " exercises the children were required to carry out more or less simple instructions with pencil and paper, in conjunction with the usual exercises in analogies, opposites, deductions, secret codes, proverbs, and absurdities. Systematic teaching of everyday words was supplementary. Evaluation of these exercises was difficult; however, the scores on Burt's Graded Direction Test, which were not regarded as satisfactory criteria, showed relatively large increases.

The cards in the " comprehension card " exercises set similar problems to the " comprehension " exercises, but the instructions were written. " Missing word " exercises were included, and some of the cards introduced difficult words for translation into the children's own vocabulary. Competition between the children was encouraged. A battery of reading comprehension tests was applied to assess the results of 3 months of these exercises, two tests by Schonell and two by Gates being included. These tests showed gains corresponding to between 7 months and 2 years in speed of comprehension. Gains in accuracy of comprehension were slight, probably because accuracy was sacrificed to some extent for the sake of the increase in speed.

Discussing these results, the author insists that improvement of reading is rarely a " purely academic problem ". The purpose of such exercises as he describes is to give the children confidence, and to help them to develop and utilize techniques of reading, which hitherto they have been unable to do because of adverse environmental factors. *D. Russell Davis*

2587. **The Identity of Alzheimer's Disease and Senile Dementia and their Relationship to Senility**
R. D. NEWTON. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 225–249, April, 1948. Bibliography.

The author points out the lack of distinguishing features between Alzheimer's disease and senile dementia. In the absence of constant signs and symptoms by means of which they can be differentiated, it seems futile to separate the conditions merely on the ground of age. In normal senility there is a process of decay which is integrated throughout the organism whereas in the dementias the process of destruction affects the cerebral nervous system before any other system. Both in normal senility and the dementias the cells seem to have lived their allotted span and death from inertia takes place. It may well be that a genetic factor is responsible for the variations in the viability of the nerve cells in different individuals and in families. Should this hypothesis be correct the conditions seen in normal senility and in the dementias would be the same except that they occur at different ages. It could also be assumed that if the brains of a random group of persons coming to necropsy were examined, the histological features of Alzheimer's disease would be found in different stages of development. The brains from 150 consecutive necropsies in a mental hospital were examined during a period of 12 months. Ages of subjects ranged from 17 to 96 and all the patients with 7 exceptions had been certified under the Lunacy Acts.

Lesions associated with Alzheimer's disease were found in various stages of development in different cases but mostly in subjects over 65 years old. They were present in many subjects between 50 and 60 years old. Where a histological diagnosis of Alzheimer's disease could be made there were no clinical features which would have helped in distinguishing the condition. In the presence of widespread lesions, however, the appearance of an organic syndrome was the rule. The functional symptoms may have to be explained as the result of an added psychosis or alternatively as the indirect result of the parenchymal lesions, being dependent moreover on the personality of the patients for quality and quantity. The remissions which have been described in the course of Alzheimer's disease are only the expression of remissions occurring in the course of a psychosis on which the histological lesions of Alzheimer's disease are superimposed. This view was confirmed by the frequent occurrence of the lesions in the cases of afferent psychosis.

The author concludes that Alzheimer's disease is a condition which appears at any age, has a definite pathological basis, and gives rise to the clinical picture of an organic syndrome. The term Alzheimer's dementia is suggested to describe this syndrome. *A. Limentani*

2588. **Stereoencephalotomy**
E. A. SPIEGEL, H. T. WYCIS, H. FREED, and A. J. LEE. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 175–177, Oct., 1948. 1 fig., 8 refs.

The stereotaxic apparatus, previously described, for the production of sub-cortical lesions in the human brain (Spiegel *et al.*, *Science*, 1947, **106**, 349) has been used in three applications. (1) Dorsomedial thalamotomy for relief of emotional tension in 16 cases: good results without undesirable reactions were obtained. (2) Mesencephalo-thalamotomy for relief of intractable pain in 2 cases: results were satisfactory but some symptoms persisted. (3) Paracommissural thalamotomy for relief of petit mal attacks in 2 cases: the grand mal attacks were not influenced, but there was remission of petit mal attacks and reduction in the accompanying motor phenomena. Electrothalamograms recorded during the operation on an epileptic patient revealed spike-and-wave discharges from the dorso-medial nucleus with no such disturbances in the records from frontal or occipital scalp. *W. Grey Walter*

2589. **The Prognosis in Schizophrenia.** [In English]
S. STENBERG. *Acta Genetica et Statistica Medica* [*Acta genet., Basel*] **1**, 5–76, 1948. 42 refs.

Most reports dealing with the prognosis in schizophrenia are open to criticism because no distinction is usually made between cases which were admitted to hospital for the first time during the period under survey and cases which had already been under hospital care for a longer time. This extensive and detailed statistical analysis deals with 1,628 cases of schizophrenia treated in a Swedish mental hospital between 1915 and 1929. Group I consists of 834 who were admitted during this period for the first time; group 2 consists of 794 patients who had been transferred to the hospital during these 15 years or were in the hospital before 1915. It was possible to follow up no fewer than 1,553 cases until 1939. None of the patients received any form of modern treatment.

The analysis of group I shows that during the first year of psychosis only 15% of men and 9·5% of women recovered, and that the probability of recovery during the second year decreased rapidly to 2·2% for men and 0·5% for women. The total probability of recovery after 10 years was 19·7% for men and 15·6% for women. Some 67% of male schizophrenics and 72% of females remained permanently ill, the rest having temporary remissions. The figures for recovery in both groups together were even lower. The difference between recovery rates of male and female patients is probably due to the fact that females with an acute schizophrenic breakdown who recover quickly are often mistakenly classified under a different diagnostic heading. The clinical analysis of permanently ill patients shows that after 10 years about 40% of male schizophrenics have predominantly catatonic symptoms; about 30% are more or less demented, and in 25% paranoid symptoms prevail. In women the division is similar but dementia is more frequent than are catatonic states. The figures indicate that in 67% of patients who have had one remission another may be expected; a high percentage of men belonging to this group have had as many as 7 remissions. It should be more widely recognized that within schizophrenia there is a fairly large number of cases with a clear periodicity. For this group of cases the time spent outside the hospital is usually twice as long as the duration of the episodes.

The statistical analysis of various symptoms shown during the first month of illness suggests that the clinical state on admission is of definite significance for the assessment of prognosis. The predominance of emotional disturbances, especially exaltation or depression, often indicates a favourable prognosis. Taken together these symptoms were seen in 49·6% of patients who ultimately recovered. The early occurrence of apathy, especially in women, points towards a poor prognosis. Delusions were more frequently met with among male schizophrenics but they were about equally frequent among those who recovered and those who deteriorated. Among women, however, the presence of delusions, particularly persecutory delusions and those of external influence, indicates an unfavourable outcome. Disorders of volition such as negativism, stereotypy, and impulsiveness were frequently encountered in cases with a poor prognosis. In women, however, catatonic symptoms were often recorded in the group which finally recovered. Confusion was not commonly met with but when present should be regarded as a favourable sign; this and other disorders of orientation were present in 22% of cases with a good outcome.

The absence of hallucinations was more common than is generally accepted. Hallucinations are of no prognostic significance. A slow and gradual beginning of the illness is an unfavourable sign; in those patients whose illness started acutely prognosis was better, especially if they were men. The prospect of a continuing improvement or permanent recovery within 10 years was 36% for men whose illness had an acute onset and only 5% for women in whom the onset was slow. No conclusions about prognosis could be made from the age of the patients at the time of their first breakdown.
J. T. Leyberg

2590. **A Hyperglycemic Factor in the Urine of So-called Schizophrenics**
L. J. MEDUNA and J. A. VAICHULIS. *Diseases of the Nervous System* [*Dis. nerv. Syst.*] **9**, 248–250, Aug., 1948. 9 refs.

Following up earlier work on the existence of an anti-insulinic factor in the blood of schizophrenic patients, experiments were undertaken in the hope of demonstrating the existence of a hyperglycaemic factor in the urine. Two methods of preparing such factor from the urine are

described. A group of schizophrenic patients was studied together with a control group of 21 males and females between the ages of 20 and 30. The hyperglycaemic factor obtained from the control group, when injected intraperitoneally into rabbits, caused an increase in the blood-sugar level of 37% at one hour and less thereafter, whereas that excreted during the same period by acute schizophrenic patients produced twice that increase. The authors state that the figures are statistically significant. The presence of the anti-insulinic factor would enable the differentiation of a group of so-called schizophrenics who exhibit symptoms suggestive of a dream-like experience. The syndrome has a good prognosis; all symptoms are reversible and respond to any of the shock therapies. *A. Limentani*

2591. **Physical Risks of Electroconvulsive Therapy**
R. KALDECK, W. F. MCLAUGHLIN, J. GURRI, and J. I. WASSERSUG. *New England Journal of Medicine* [*New Engl. J. Med.*] **239**, 773–779, Nov. 18, 1948. 9 refs.

This report is based on the observation of 628 patients who received 8,082 electric-shock treatments. The age of the patients did not appear to be a contraindication, but it should be noted that the series included only 5 patients over 70 years of age. Severe malnutrition was not a contraindication. In 50 patients there was evidence of cardiovascular disease, such as arteriosclerosis, hypertension, abnormal electrocardiographic findings, and rheumatic disease of the heart. One patient had had a coronary thrombosis. All these patients were treated without ill effects. The authors recommend caution in the treatment of patients with tuberculosis as there seemed to be definite risks involved. Selected cases of active tuberculosis were nevertheless treated with success. The authors concur in the current view that any infection is a contraindication. The only death in the series occurred in a man who, at necropsy, was found to have had acute glomerulonephritis and acute focal myocarditis. There were 11 cases of fracture, including 2 in patients with previous bone disease. Nine patients with histories of fractures before treatment were given electric convulsion therapy without untoward effects, but one patient with ankylosis of the elbow sustained a fracture of the humerus. [It is not stated whether a routine radiograph of the spine was taken on completion of treatment.] The series included a few patients with diseases of the central nervous system and 5 patients with diabetes mellitus. *A. Limentani*

2592. **Thyroid Therapy in Some Mental Disorders**
L. DANZIGER and J. A. KINDWALL. *Diseases of the Nervous System* [*Dis. nerv. Syst.*] **9**, 231–241, Aug., 1948. 55 refs.

The rationale of the experiments described in this paper is based on the assumption that cerebral anoxia is common among patients suffering from psychiatric disorders. Anoxia is often associated with deficiency of the adrenal cortex and thyroid. Anoxia may be responsible for the occurrence of relapses after electric convulsion therapy, which is known to increase cerebral oxygen consumption. Good results could be expected to follow thyroid medication as part of a multiple attack on the anoxia. Intensive thyroid medication was carried out in 24 patients (19 of them psychotic and 5 psychoneurotic). Insulin or electric convulsion therapy was given at the same time in the majority of cases, together with large doses of vitamin B. In half the cases the basal metabolic rate was normal at the start, but in every case either the basal metabolic rate or the blood-cholesterol estimations pointed to reduced thyroid activity. As a result of the treatment all patients improved and 21 recovered. The authors claim that large doses of thyroid were well tolerated and that electric convulsion therapy appeared to be synergistic with thyroid treatment. It is also claimed that no patient in the series relapsed unless he stopped taking the thyroid or his basal metabolic rate was allowed to fall. Technique and clinical details are given. *A. Limentani*

2593. **Leucotomy in the Treatment of Psychopathic Feeble-minded Patients in a State Mental Deficiency Institution**
G. W. MACKAY. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 834–843, Oct., 1948.

Leucotomy was performed under local analgesia on 14 women and 6 men, of whom 2 were epileptics and 5 post-encephalitics. All patients showed evidence of psychopathic personality, many having been extremely violent for several years. The mental ages of 3 of the patients were 4, 7, and 12 years. The duration of observation after operation in 5 cases given in detail varied from 10 to 18 months. Of the women, 6 recovered or considerably improved, and 5 improved; of the men, 1 considerably improved, 2 improved, and 1 died. Improvement in some cases did not occur immediately after the operation. The author considers that leucotomy gives no marked permanent benefit when a definite paranoid attitude is present; one schizoid paranoid patient deteriorated after the operation.
G. de M. Rudolf

2594. **The Effect of Leucotomy on Creative Personality**
E. L. HUTTON and M. BASSETT. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 332–350, April, 1948. 6 figs.

Early work with the Rorschach test has shown that persons lack creativity after leucotomy. The application of the multiple choice method (Harrower–Erickson) confirmed the results obtained with individual tests. According to the authors there are at least four factors involved in creative activity: (1) imagination; (2) emotional motives; (3) technical knowledge and practical ability; (4) sustained effort and persistent application. The last two factors are known to be little affected by leucotomy. Does the section of the prefrontal fibres destroy the power to create or does it affect the emotional factors which normally motivate creativity? To investigate this problem the authors have used, in addition to the Rorschach test, a story-telling test in which the subjects are asked to write 8 stories, introducing one given sentence into each story, and a drawing test consisting of 8 items.

So far it has been difficult to show how the creative activity is influenced by the leucotomy as few of the patients investigated had shown real evidence of creativity before operation. Such ideal conditions existed in one case studied and reported in full by one of the authors. The patient before the operation had shown evidence of creative spirit in her poems, prose, and dramatic work. During the first 9 weeks after leucotomy the results of the investigation suggested that creative imagination was practically non-existent. Emotional motives and associated judgments of value were not apparent. There was a decrease in effort and application. It remains to be seen whether some or all such changes are permanent.

A. Limentani

2595. **Prefrontal Leucotomy in Mental Defectives**
M. ENGLER. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 844–850, Oct., 1948. 29 refs.

Results are reported in 43 cases in which prefrontal leucotomy was carried out. The ages of the patients ranged from 17 to 47 years, the average being $27\frac{9}{12}$ years. All grades of deficiency were treated, but 75% were low-grade imbeciles and idiots. All were restless, excitable, irritable, destructive, wet, and dirty, frequently had screaming fits for hours or days, and often resorted to self-mutilation or were so violent as to be a permanent menace to staff or patients. The cases were observed for from $1\frac{1}{2}$ to 3 years following operation.

Of the 43 patients, 5 died between 1 day and 1 year after operation. Of the remaining 38, in 4 the frequency and severity of the epileptic fits considerably increased, while 3 more developed fits for the first time after operation. Three patients showed remarkable improvement; in one this was apparently due to the release of a large amount of fluid. One of the 2 other patients had had a paranoid psychosis with screaming fits and had been extremely troublesome and abusive. Nearly 2 years after the operation she worked well but was noisy and troublesome at times, although incomparably better. The other patient, a schizoid individual subject to fits of screaming persisting for several days, has been well behaved for nearly 3 years. Of the 38, 7 showed slight or very slight improvement, 13 were unchanged, and 12 became worse or much worse. Three others deteriorated so greatly that they were certified under the Lunacy Act, one becoming hallucinated. One other improved remarkably for 5 months and then gradually became unmanageable, threatening, and dangerous.

The great majority of the patients who improved came from the higher grades. Many were quiet and well-behaved for weeks or months after the operation, but gradually returned to their former condition. The author suggests that this quietness is due to the shock of the operation on the nervous system. At a later date other paths may take over the function of those destroyed by the operation. The author points out that the brains of defectives are seldom normal, and estimates that in 9 out of 10 low-grade defectives the thalamo-frontal radiation will not be cut properly. His view is that leucotomy should not be undertaken in low-grade defectives, and that only defectives who possess a relatively high-grade level of intelligence and, in addition, a high standard of personality are likely to benefit without too great a deterioration in mental level and personality.

G. de M. Rudolf

2596. **The Results of a New Method of Prefrontal Lobotomy.** (A praefrontalis lobotomia mütéti eredményei új eljárás segítségével)
J. SATTLER. *Orvosok Lapja* [*Orv. Lapja*] **4**, 1321–1324, Oct. 10, 1948. 4 figs., 5 refs.

In his method of prefrontal lobotomy the author employs electro-cauterization not only of the centrum ovale but also of the grey matter. There is no haemorrhage during or after the operation, and the results are claimed to be superior to those obtained by other methods.

The point of intersection is determined of the semicircles (*a*) between the bridge of the nose and the inion, and (*b*) between the zygomatic processes. The incision is made in a line 4 cm. long parallel to the sagittal sinus, 2 to 3 cm. inwards from the point mentioned above. If the incision is made correctly, the coronal suture appears after the periosteum is removed. Trephining is carried out 1·5 cm. anterior to the coronal suture. The opening on the inner side of the skull is given an oval shape by use of a spoon, in order to facilitate the introduction of the instrument at a certain angle. A part of the dura which is not injected should be chosen for the incision, which is made with a von Graefe knife. The cautery is first introduced parallel to the sagittal sinus, progressing towards the dura, and on withdrawal the white matter is cauterized again. The second time the cautery is directed laterally, and lastly towards the base. The cautery is withdrawn with slight "oscillating" movements. The cauterization should affect the entire thickness of the frontal lobe, and be carried out on either side in each of the 3 directions mentioned at least at 3 points. The operation, which can be performed in quiet patients under local analgesia, lasts for 25 to 30 minutes. In 3 cases epileptic fits of Jacksonian type occurred during the operation; the cautery was removed and the operation completed after the end of the fit. Disturbance of the function of the sphincter ani was observed in a few cases for 10 to 14 days and disappeared without special treatment. Between April 1, 1947, and January 1, 1948, 70 patients were subjected to the operation. One died within 24 hours of the operation. The following table shows the results in the others.

Diagnosis	Cured	Improved	Unchanged
Various forms of schizophrenia ..	21	17	16
Epilepsy	—	4	1
Melancholia ..	3	1	—
Paranoid depressive climacteric hypertension ..	3	1	1
Migraine	2	—	—

Vilma Samet

Infectious Diseases

VIRUS INFECTIONS

2597. **Methods of Protection against Homologous Serum Hepatitis. I. Studies on the Protective Value of Gamma Globulin in Homologous Serum Hepatitis SH Virus**
J. STOKES, M. BLANCHARD, J. R. NEEFE, S. S. GELLIS, and G. R. WADE. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 336–341, Oct. 2, 1948. 10 refs.

Hepatitis may be produced in human volunteers by the virus of infective hepatitis (IH), which has an incubation period of 18 to 40 days, or by a virus (SH) present in human serum, this condition having an incubation period of 60 to 150 days. There is still controversy as to whether the two viruses are or are not identical. Gamma globulin obtained from large pools of human serum has had protective effects during the recent war in four widely separated epidemics of infective hepatitis. Similar inhibitory effects have been reported in connexion with the virus of serum hepatitis (SH), although they were less marked and two 10-ml. doses of gamma globulin were required. In another study, in which only one dose was used, there was no difference between experimental and control groups.

In experiments reported in this paper, known icterogenic plasma was used together with gamma globulin. In the first experiment, in which virus and globulin were administered simultaneously to volunteers, hepatitis developed with no difference between incubation periods in the treated and control groups. In the second the virus was of very low potency and no actual jaundice developed, but the globulin administered one, two, or three months after infection did appear to protect. In the third, a similar plan was followed with 7 volunteers in each group, but gamma globulin again had no significant protective power. In other experiments convalescent serum from a case of serum hepatitis was employed, but there was also no protection. In view of these results it would appear probable that the IH virus is not the same as the SH, and that IH virus and the antibody are widespread in the population, but that SH and its antibody are less common. *R. Hare*

2598. **Methods of Protection against Homologous Serum Hepatitis. II. The Inactivation of Hepatitis Virus SH with Ultraviolet Rays**
M. C. BLANCHARD, J. STOKES, B. HAMPIL, G. R. WADE, and J. SPIZIZEN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **138**, 341–343, Oct. 2, 1948. 15 refs.

In view of the danger of producing serum hepatitis by the injection of pooled human plasma or serum, methods have been sought to prevent this. Amongst other methods, exposure to ultraviolet light has been employed, but the results were somewhat inconclusive. In the present paper the authors report a new study of the problem.

The virus used was contained in a pool of human serum collected from volunteers during the early stages of experimentally produced serum hepatitis and 6 months before the experiments reported had produced hepatitis in 50% of the volunteers. The serum pool was irradiated in a Habel–Sockrider apparatus, with a rate of flow of 24 ml. per minute, by means of a lamp having an intensity of 3,500 microwatts per square centimetre and operating at a distance of up to 9 mm. Approximately 85% of the irradiation was in the 2,537 Å wave-length. The time of exposure of the serum was 10 seconds and the thickness of the film 0·263 mm.

Fifteen volunteers served as controls, 11 receiving 4 ml. of non-irradiated serum intramuscularly. Four received 2 ml. of serum and 10 ml. of convalescent plasma taken from a patient 2½ months after the illness; they were also given 20 ml. of convalescent plasma 1, 2, and 3 months later. Eleven volunteers received 7 ml. of the irradiated serum. Of the 11 volunteers receiving control material, 2 became ill with hepatitis and jaundice after 77 and 80 days respectively. One had hepatitis without jaundice after 87 days, and 3 had mild hepatitis without jaundice after incubation periods of from 73 to 80 days. Their symptoms comprised malaise, lassitude, anorexia, nausea, occasional vomiting, and discomfort in the right upper quadrant of the abdomen, but there were no significant changes in the liver-function tests employed. Of the other 4 controls, 1 had jaundice with an incubation period of 93 days. In the group of 11 volunteers who received irradiated serum there were no signs of jaundice or hepatitis.

There is therefore a possibility that irradiation of serum or plasma pools might inactivate the virus of serum hepatitis, but it is also obvious that, in view of the relatively low incidence of frank jaundice in the control group and the fact that other workers have failed to inactivate the virus by means of ultraviolet light, much further work will be necessary before this method can safely be adopted as a routine. *R. Hare*

2599. **Complement Fixation Reactions in Psittacosis**
D. J. DAVIS. *Archives of Internal Medicine* [*Arch. intern. Med.*] **81**, 623–629, May, 1948. 1 fig., 11 refs.

A complement-fixation test with psittacosis antigen was performed on samples of sera from an unspecified number of patients suspected to be suffering from psittacosis, and a positive reaction in significant titre was obtained in 21 cases; in 9 of these there was at least a fourfold rise in titre during the illness, and in 12 the reaction was positive in a titre of at least 1 in 32 when the serum was first examined. All these patients had a pneumonia-like

illness, with radiological evidence of pulmonary lesions in 12 out of the 16 in whom a radiograph of the chest was taken, and all gave a history of intimate contact with birds, usually pigeons or parakeets. Psittacosis virus was isolated from the sputum of one patient and from birds kept by 3 others. None of these patients gave a history of venereal disease or positive reactions to serological tests for syphilis. [It is known that infection with the virus of lymphogranuloma venereum may produce a positive complement-fixation reaction with psittacosis antigen.] The complement-fixation test yielded positive results about 7 to 10 days after the onset of the illness; the highest titre was reached about 15 to 30 days after the onset; and a positive reaction persisted for as long as the serum was tested, in one case for nearly 2 years.

[This paper shows that, when the complement-fixation test with psittacosis antigen is positive in significant titre, the history and clinical findings are in keeping with the diagnosis of psittacosis. It throws no light on the frequency with which patients with psittacosis may be expected to give positive complement-fixation reactions.]

A. R. Kelsall

2600. **Herpes Zoster Following Exposure to Varicella: Treatment of Herpes Zoster with Cowpox Vaccine**

S. H. HORTON. *United States Naval Medical Bulletin* [*Nav. med. Bull., Wash.*] **48**, 742–749, Sept.–Oct., 1948. 25 refs.

The author gives a fairly complete review of the clinical literature on the epidemiological connexion between varicella (chickenpox) and herpes zoster. [Although many instances of such an association have been recorded since von Bókay's original observations, none of them, including those adduced by the author, amounting merely to 3 cases of zoster following exposure to zoster or varicella or both, furnishes definite proof of an identical aetiology. No reference is made to serological and virus investigations, notably those recorded in 1934 by Amies, who concluded that both diseases were due to closely related strains of " elementary bodies ".] The chief interest of the article, however, lies in the use of vaccination (with cowpox material) in the treatment of herpes zoster; this has apparently been reported only once before by Lillie in 1943. A series of 4 to 6 vaccinations daily or every second day gave usually " accelerated " and occasionally " immune " reactions, which were held to influence the primary disease favourably. [As there were no control experiments, and all 3 patients were young healthy naval ratings, little faith can be put in the claims confidently made. Details of the antigen and method of inoculation are not given. The high proportion of accelerated reactions (which are presumably modified " takes ") would appear to suggest inadequate protection against smallpox in these personnel who presumably had been vaccinated since joining the service; alternatively, the interpretation of reactions observed was different from that usual among vaccination experts. Among other inaccuracies, the date of von Bókay's first publication is given as 1892 although the only reference is to an article which appeared in 1924, and Fife is placed in Switzerland.]

William Gunn

2601. **Herpes Zoster Following Operations for Facial Pain. A Clinical Investigation on 830 Cases.** [In English]

L. EPSTEIN. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] **23**, 13–48, 1948. Bibliography.

The not infrequent occurrence of herpes zoster after operations for the relief of facial pain provides an opportunity for the study of the pathogenesis of this condition. Head and Campbell thought that the site of the nervous lesion in zoster was the spinal ganglia, but subsequent workers have indicated that the damage is more widespread.

From the 830 operations providing the material for study 58 cases of peripheral nerve section and alcohol injection were excluded because of the short stay in hospital. The incidence of herpes zoster in the series was 18·5%; 55·4% had a temporal root section, 23·6% developing herpes; 21·4% were subjected to Dandy's operation, with an incidence of 15·1% of herpes; 14% had a tractotomy and 7·3% developed herpes. Of 9 patients who underwent operation on the sympathetic pathways none developed herpes. Herpes zoster appeared twice as frequently after subtotal as after total operations, the incidence in 64 cases of total root section being 14·1% against 26·4% in 345 subtotal sections. For Dandy's operation the figures were 7·1% and 16·1% respectively. It seems, therefore, that the preservation of some fibres facilitates the subsequent appearance of herpes. If damage to the Gasserian ganglion was the only factor concerned in causing herpes zoster, this difference between total and subtotal operations would not be expected. The degree of trauma at operation had a significant effect on the incidence of zoster. The post-operative course, however, had no influence on the incidence of herpes except as regards febrile meningo-cerebral complications, which occurred in 9·2% of the herpetic cases but in only 2·9% of the non-herpetic cases, suggesting that post-operative herpes zoster may be due to activation of a latent virus throughout the nervous system.

The herpetic vesicles appear almost always in the areas supplied by second and third divisions of the trigeminal nerve. The areas affected appear to have no relation to the type or extent of section of fibres. Damage to the motor root appeared in 25·7% of herpetic cases but in only 14·4% of non-herpetic cases. However, sympathetic damage appeared in only one case of herpes.

From these observations it becomes clear that the Gasserian ganglion is not the only site at which the infliction of trauma will produce herpes zoster. Nor can trauma with its subsequent oedema, haemorrhage, and degeneration be the sole cause of the herpes, for the occurrence of febrile meningo-cerebral complications and of herpes outside the territory of the severed nerve suggests an inflammatory process, possibly due to a specific virus. The appearance of post-operative herpes in only 18·5% of the cases does not exclude the presence of a specific virus in all.

The hypothesis that the zoster results from the loss of " trophic " fibres is also not supported by this study, for with total section the incidence of herpes was only half

that with subtotal section. Moreover, herpes appeared in areas of normal sensibility after operation, and tractotomy relieved herpes in an area rendered completely anaesthetic by a previous root section. Suggestion is made, therefore, that the site of surgical trauma serves as an " irritable focus " which puts a higher centre in a state of hyperirritability. From this centre efferent impulses travel, possibly along sympathetic pathways, and produce the eruption in the skin. This theory accords with the clinical observations in that the greater the trauma the more " irritable " the focus will become. Also temporal root section will be associated with a greater incidence of herpes because of the proximity of the Gasserian ganglion, disturbance of whose cells increases the hyperirritability of the central focus. Subtotal section will more easily predispose to herpes by leaving some fibres along which the impulses can travel to irritate this central focus. It seems that spontaneous herpes may also be explained on the same basis. The failure of operation on the first sensory neurone to relieve the neuralgia which accompanies this condition points to a higher centre as the hyperirritable focus causing the pain and releasing the herpes zoster. *Fergus R. Ferguson*

2602. **Isolation of Mumps Virus from the Blood of a Patient**

L. KILHAM. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 99–100, Oct., 1948. 3 refs.

Blood withdrawn from a patient with mumps on the day parotitis was first observed was treated with 0·5% sodium citrate. The red cells were allowed to settle by natural sedimentation, the plasma was separated, and both fractions were stored in dry ice for 14 days. Eggs after 7 days' incubation were employed, and 0·1 ml. of the plasma inoculated intra-amniotically and 0·2 ml. of the cellular fraction diluted 1 to 2 were inoculated into another 12 eggs.

Amniotic fluid from each egg was examined for macroscopic agglutination of hen erythrocytes, and at the third passage virus was detected in 4 out of 8 fluids and in almost all the eggs of subsequent passages. (Since only 3 embryos survived in the group inoculated with cells, the material from these eggs was pooled with the remainder and it is therefore impossible to state whether the virus was predominantly in the plasma or cells.) No virus was detected in the cerebrospinal fluid and no attempts were made to isolate it from the saliva. No virus was isolated from the blood of 7 other patients examined during the first 5 days. The virus was identified by inhibition of haemagglutination and complement-fixation tests with pooled amniotic fluid, serum from patients in the acute and convalescent phases of mumps being used, while the clinical diagnosis of mumps in the patient was confirmed by a rise in titre of the haemagglutination-inhibiting antibody, the Enders strain of virus being used as antigen. Mumps virus has been isolated from 5 (or possibly 7) cases of meningo-encephalitis in which cerebrospinal fluid was examined within 5 days of onset. *R. Hare*

POLIOMYELITIS

2603. **Impairment of Pulmonary Function in Poliomyelitis. Oximetric Studies in Patients with the Spinal and Bulbar Types**

J. O. ELAM, A. HEMINGWAY, G. GULLICKSON, and M. B. VISSCHER. *Archives of Internal Medicine* [*Arch. intern. Med.*] **81**, 649–665, May, 1948. 8 figs., 16 refs.

During an epidemic of poliomyelitis the Millikan-Smaller oximeter was used to investigate the nature of disturbances in respiratory function in 43 patients; illustrative records of 8 cases are given. The oximeter measures continuously changes in oxygen saturation of the blood in the warmed ear lobe, and it is thus possible to study the effect of mechanical respiration and of the administration of oxygen in varying percentages, by mask and by tracheotomy tube, with and without positive pressure. The authors divide disturbances of respiratory function in poliomyelitis into two main types—ventilatory deficiency and alveolar deficiency. The former occurs with paralysis of the diaphragm or intercostal muscles and with depression of the respiratory centre; the latter results from local lesions in the lungs, such as oedema, atelectasis, and pneumonia. In pure ventilatory deficiency oximetric readings show that normal oxygen saturation of the blood can be maintained by efficient mechanical respiration alone, whereas in pure alveolar deficiency the administration of adequate oxygen without mechanical respiration will suffice; in cases of mixed ventilatory and alveolar deficiency, both mechanical respiration and the administration of oxygen will be necessary. The oximeter is also useful in gauging the response of the patient to periods of cessation of oxygen therapy or mechanical respiration, since minor degrees of anoxaemia thus revealed may give no clinical symptoms or signs. It was found that anoxaemia may develop rapidly in a patient in a mechanical respirator when the ports are opened for nursing attention, and that this may be delayed by the administration of 100% oxygen by mask for a period of 5 minutes before and during the opening of the ports. Similarly, in patients with bulbar involvement who are treated by oxygen inhalation through a tracheotomy tube, the administration of 100% oxygen by mask may minimize the anoxaemia which develops during the removal of secretions by suction through the tube. *A. R. Kelsall*

2604. **Experimental Studies of Variables in Neutralization Tests with Lansing Poliomyelitis Virus**

E. J. BELL. *American Journal of Hygiene* [*Amer. J. Hyg.*] **48**, 381–393, Nov., 1948. 2 figs., 18 refs.

Many investigators, using the Lansing strain as antigen, have studied antibody levels in man and animals, the titrations being performed in mice by cerebral inoculation. This paper describes a series of observations relating to various questions of technique.

(1) In serum neutralization tests it is customary to make the virus dilutions in a diluent containing a protective serum protein such as broth or serum-saline, to prevent a considerable drop in virus titre. However,

with the Lansing virus no difference was observed in the 50% mortality end-points obtained when either physiological saline, distilled water, or 10% monkey serum was used as a diluent. Further, it was found that there was only a 2-fold (0·3 log.) decrease in virus titre when mixtures were incubated at 37° C. for 2 hours and then for 20 hours at 4° C. The virus therefore appears to be fairly stable.

(2) Experiments were next performed to check the effect of time and the temperature of incubation on the LD 50 of virus alone without admixture with antiserum. Numerous titrations were carried out under three different conditions: room temperature for 15 minutes before inoculation of mice; room temperature for 1 hour; and 37° C. for 2 hours. The findings suggested that there was no significant fall in titre of virus under these conditions.

(3) There has been considerable discussion whether apparent neutralization of virus in virus–immune-serum mixtures *in vitro* occurs almost immediately, or whether neutralization increases with prolongation of interaction. There was a general and consistent trend toward increasing serum titres as the temperature or time of incubation of the mixtures was increased. However, only approximately 0·3 log. difference was observed between the mean serum titre obtained after incubation of mixtures for 1 hour at room temperature and that obtained after incubation for 2 hours at 37° C.

(4) A linear relationship was found to exist between the logarithm of the 50% neutralization end-point of serum and the logarithm of the quantity of virus employed in determining this end-point. For each approximate 3·2-fold (0·5 log.) increase in virus used in a serum titration there was a corresponding 2·5-fold (0·4 log.) decrease in the resulting serum titre.

(5) As regards reproducibility of results, when 10-fold serial dilutions of serum were tested the maximum difference in titre was found to be 0·4 log.; with 3-fold dilutions the range was within 0·2 log. *A. J. Rhodes*

2605. **Immunization of Monkeys with Formalin-inactivated Poliomyelitis Viruses**

I. M. MORGAN. *American Journal of Hygiene* [*Amer. J. Hyg.*] **48**, 394–406, Nov., 1948. 27 refs.

As an introduction to this work the author, from her previous studies on the active immunization of monkeys with inactivated virus vaccines, concludes that in general the evidence for conferment of a significant degree of resistance is slight. Effective immunization has, however, been achieved with the Lansing strain in mice and cotton-rats.

Vaccines were prepared from the cervical and lumbar enlargements of monkeys killed on the first day of paralysis. Studies were carried out on the rate of inactivation of Lansing virus in the presence of nerve tissue by 0·1%, 0·3%, and 0·5% formalin at 4° and 37° C. After 3 hours at 37° C. virus could no longer be detected by inoculation of mouse or cotton-rat. At 4° C. virus " passed the threshold of detectability " in mice between 6 and 7 days. On the basis of a preliminary test it was decided to use a vaccine prepared at 4° C. in 0·3% formalin; the vaccine employed was no longer infective on intracerebral injection in monkeys.

(1) Seven rhesus monkeys were each given 10 intramuscular injections of Lansing monkey-cord virus inactivated by formalin over 19 weeks. These monkeys, in vigorous physical condition, and 3 normal controls were then injected intrathalamically with about 6,000 PD 50. The 3 controls, and also 2 of the 7 vaccinated animals, became paralysed. Four of the remaining 5 showed some weakness, but in all 5 no histological evidence of poliomyelitis was found.

(2) None of the monkeys had demonstrable serum antibody before vaccination; 5 out of 7 had measurable antibody when tested at 4 weeks (after 3 injections of vaccine). By 9 weeks all the monkeys had neutralizing antibodies. The titres continued to rise up to 12 weeks, but fell during a 6-week rest period. There was, however, a marked rise by 8 days after a single additional " booster " dose. One of the 2 vaccinated animals that died after the test inoculation had a far lower antibody level than the rest of the group, but the other animal had an antibody level at the time of the " challenge " inoculation not distinguishable from that of the other 5.

(3) Vaccination was attempted with another strain of virus—the Brunhilde—which was isolated from human stools collected in Baltimore in 1939. Five rhesus monkeys were given 9 doses of vaccine by the intramuscular route over a period of just under 3 months; each animal received approximately 1,000,000 LD 50 in the course of vaccination. They were subsequently inoculated by thalamic injection of 5,000 PD 50; one animal was found dead 2 days later, presumably owing to trauma or other cause unrelated to the virus " challenge ". Of the remaining 4, one became paralysed. It has thus been shown that the intramuscular injection of formol-inactivated Lansing or Brunhilde viruses can confer a significant degree of protection on rhesus monkeys when a large dose of virus is given intracerebrally. *A. J. Rhodes*

See also Section Hygiene, Abstract 2206.

RICKETTSIAL INFECTIONS

2606. **Rickettsialpox**

H. M. ROSE. *New York State Journal of Medicine* [*N. Y. St. J. Med.*] **48**, 2266–2271, Oct. 15, 1948. 9 refs.

Rickettsialpox was first recognized in 1946 and it has not been reported from any area outside New York City. It is caused by *Rickettsia akari* and is probably transmitted by the rodent mite (*Allodermanyssus sanguineus*) from its reservoir, the common house mouse (*Mus musculus*) to man. More than 350 cases have been reported, and the author describes a further 21 seen during one year, 17 of which have been studied. A primary skin lesion is followed about a week later by fever, chills, headache, malaise, and an eruption resembling chickenpox. The illness lasts about a week and is not fatal. The period of incubation is unknown.

The author observed that at the point of the insect bite an area of induration and erythema about 1 to 2·5 cm.

in diameter developed. There was early a large central cloudy vesicle and later on a dark brown or blackish central crusted area. The lesion was not painful; it was occasionally multiple. Drainage lymph nodes were enlarged and tender but there was no lymphangitis. Within a week fever developed with rigors, chiefly frontal headache, backache, and muscle aches. The temperature was usually from 101 to 105° F. (38·3 to 40·6° C.) and intermittent, settling by lysis within a week. Splenomegaly was uncommon (3 out of 17 cases). Within 2 to 7 days of onset of the febrile phase a maculo-papular rash developed, generally distributed over the body including the face and the soles and palms. Vesiculation occurred commonly, vesicles either having small centres or being identical with those seen in chickenpox. The rash was non-irritant and was followed by brownish pigmentation but no scars. In 5 of the 17 cases similar lesions appeared on the buccal mucosa but lasted under 48 hours.

The differential diagnosis is from chickenpox—the eruption is similar; from infective mononucleosis—the blood film may be similar; from murine typhus and Rocky Mountain spotted fever, but there is no primary lesion and the rash is dissimilar. [Smallpox is not mentioned but the author does not make it clear why atypical smallpox cannot be confused with this disease.]

In nearly all the patients there was leucopenia, often with a normal differential count, but occasionally large mononuclear cells with vacuolated cytoplasm resembling the cells seen in infective mononucleosis were observed. Weil–Felix agglutination tests with OX19 and OXK were negative, but a specific complement-fixation test is described in which rising titre indicated a positive result.

Treatment of rickettsialpox is non-specific, and where streptomycin was tried in the present cases it was without effect. *John Anderson*

2607. **Effect of *para*-Aminobenzoic Acid upon the Clinical Course, Rickettsemia, and Development of Complement-fixing Antibodies of Murine Typhus in the Guinea Pig**
J. F. SADUSK, C. HJERPE, and M. FREEDMAN. *American Journal of Tropical Medicine* [*Amer. J. trop. Med.*] **28**, 673–682, Sept., 1948. 16 refs.

The effect of *para*-aminobenzoic acid (PABA) on murine typhus in the guinea-pig was studied in two experiments. The infective material consisted of a 10% suspension of infected guinea-pig tunica vaginalis and testes in sterile skimmed milk at *p*H 7·3, stored under CO_2 ice, an intraperitoneal dose of 0·5 ml. being used. In the first experiment 10 animals were divided into two groups: group A (6 guinea-pigs) received PABA orally, and 1·5 ml. of 20% sodium PABA thrice daily subcutaneously, for 5 days: group B received, in addition to oral PABA, 1 ml. of 20% sodium PABA subcutaneously at the same intervals for the same number of days. The animals were infected 4½ hours after the first dose of PABA. There were 6 untreated controls. The 6 animals in group A died, presumably as a result of overdosage of PABA; 3 of the 4 animals in group B survived, the fourth died of PABA toxicity. None of the PABA-treated animals developed fever, and a scrotal reaction was found in only one, in contrast to a 100% incidence of fever and scrotal reaction in the controls. Rickettsiaemia and complement-fixing antibodies developed at the same time and to the same degree in both treated and untreated groups.

In the second experiment there were 14 guinea-pigs, 7 serving as controls. In the test animals a combination of oral and subcutaneous PABA was again used, 1·5 ml. of a 20% solution of sodium PABA being given subcutaneously twice daily. Treatment lasted for 5 days, including the day of inoculation. The results obtained in the first experiment were confirmed. Thus, 2 of the test animals developed a scrotal reaction, fever occurring in only one of these, while fever and a scrotal reaction were observed in all of the controls. Three of the treated animals died with clinical signs of PABA toxicity. Both groups of animals developed complement-fixing antibodies at the same time and in the same titre, and the animals of both groups showed rickettsiaemia. It is evident, therefore, that PABA prevents the development of clinical signs of murine-typhus infection, but permits the appearance of circulating rickettsiae and complement-fixing antibodies. It is suggested that the drug acts by controlling the severity of the infection until there is sufficient immunity to dispose of the infecting organisms. The mechanism of action is possibly by the blocking of an enzyme system. Details of PABA concentrations in the blood are given. No substances were found in the blood of untreated guinea-pigs which gave the colour reaction of PABA. *J. L. Markson*

2608. **Cross-immune Reactions between Panamanian Strains of Q Fever and Endemic Typhus**
E. C. DE RODANICHE. *American Journal of Tropical Medicine* [*Amer. J. trop. Med.*] **28**, 683–686, Sept., 1948. 4 refs.

Guinea-pigs inoculated intraperitoneally with the J.D. strain of *Coxiella burnetii* (Q fever) and inoculated 17 to 43 days later with the S.M. strain of murine typhus showed the following evidence of partial immunity to the latter strain: 6 of 12 guinea-pigs gave definite febrile reactions, compared with 9 of 12 controls not immunized by the Q fever strain; only 2 of 12 Q-fever immune animals developed a moderate testicular reaction, whereas a moderate to severe reaction occurred in 9 of 12 controls. In reverse cross-immunity experiments, guinea-pigs previously inoculated with the S.M. strain of murine typhus, showed a partial immunity against the J.D. strain of Q fever, indicated by a definite prolongation of the incubation period and shortening of the febrile period. Complement-fixation tests with immune guinea-pig serum and yolk-sac antigens failed to yield significant cross-reactions. *J. L. Markson*

2609. **Complement Fixation in Human Sera Following Murine Typhus**
E. R. RICKARD. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 31–34, Oct., 1948. 8 refs.

Specimens of sera were obtained from 404 individuals who had had fever and contact with rats, and who on

epidemiological evidence could have contracted typhus. They could be divided into 6 groups on the bases of the occurrence of a rash and of previous positive Weil–Felix reactions. The sera were collected at intervals varying from 7 days to 3 years 11 months after onset of illness, and were stored in the cold for periods varying from 7 days to 4 months before examination. Complement-fixation tests were carried out with 3 units of amboceptor, 2 units of complement, and 2 units of antigen—the latter consisting of embryo yolk sacs infected with the Wilmington strain of murine rickettsiae, from which lipids were extracted by benzol and ether and the antigen purified by sodium sulphate precipitation. Results were positive in titres ranging from 1 in 2 to 1 in 128 in 313 sera, and negative in 91. The negative sera were also negative when tested against rickettsiae of Rocky Mountain fever. Positive results were also analysed on the basis of the interval between onset of the disease and taking of the specimen, divided into 1 year periods. While positive results were more common when the Weil–Felix agglutination titre had previously been 1 in 320 or more, whether or not a rash was present, than in the case of individuals with a lower titre, the mean positive titres in these groups were similar, being 1 in 21 and 1 in 22 respectively. Similarly there was no significant effect on the mean positive titre of increasing lapse of time between the illness and collection of the specimen. With the exception of a few reactions at the lowest dilution (1 in 2) in controls, the test was found to be specific. *G. T. L. Archer*

BACTERIAL INFECTIONS

2610. **Peripheral Neuropathy in Neural Leprosy. Report of a Case**
J. PESSIN and C. F. KITTLE. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **60**, 288–296, Sept., 1948. 4 figs., 6 refs.

The case is described of an Italian, aged 57, who had a slowly developing neurological disease over the course of 20 years with, in the earlier stages, weakness and atrophy of the small hand muscles, right foot-drop, and a left facial palsy. As the disease progressed weakness of all four limbs developed, together with complete loss of pain and temperature sensation and diminution of light touch sensation over the whole body except the scalp. There was no thickening of the peripheral nerves and no cutaneous lesion except for brown pigmentation of the legs and the scars of painless burns. Twenty years after the first symptoms the diagnosis of leprosy was made by examination of a smear from a superficial ulcerated area in the anterior part of the nose, in which Hansen's bacilli were found. On a previous occasion many microscopical preparations of skin from the trunk and abdomen had been examined without the bacilli being found. The man had lived in Brazil for several years during the earlier part of his life.

The authors discuss the differential diagnosis between syringomyelia and leprosy, stressing that the former is a cord disease and the latter essentially a peripheral neuropathy. They state that examination of skin sections frequently fails to demonstrate lepra bacilli in established cases of the disease, and stress the value of smears from nasal lesions in making the diagnosis.

J. W. Aldren Turner

2611. **Penicillin in Diphtheria. Report of a Subcommittee of the Public Health Laboratory Service**
R. CRUICKSHANK, E. H. GILLESPIE, W. GOLDIE, H. J. HARRIS, W. H. H. JEBB, G. J. G. KING, P. H. MARTIN, M. T. PARKER, and A. MACDONALD. *Lancet* [*Lancet*] **2**, 517–519, Oct. 2, 1948. 1 fig., 5 refs.

The penicillin sensitivity of 284 strains of *Corynebacterium diphtheriae*, isolated in different parts of Britain, was tested, and an attempt was also made to find out whether penicillin treatment shortened the time of carriage of the organism in acute cases of faucial diphtheria, or aided its elimination from persistent throat carriers. The clinical effect of penicillin on diphtheria was not considered.

For each strain of *C. diphtheriae*, a range of 6 tubes was put up and inoculated in nutrient broth (*p*H 7·5), containing 1% "lab lemco", 1% proteose peptone, 0·5% sodium chloride, and 5% of a single batch of heat-inactivated, Seitz-filtered horse serum; 5 ml. of this broth was used for each of the dilutions of penicillin, these ranging from 0·6 to 0·03 unit per ml. of medium. Each tube was inoculated with an arbitrary standard loopful (4 mm. internal diameter) of an overnight culture of the organism grown in the same medium and incubated for 24 hours at 37° C. A control series of tubes was inoculated with the Oxford staphylococcus. Tubes were examined for turbidity, and from the tube at the visual end-point and from the tube with the next highest penicillin concentration a standard loopful was spread on half a blood–agar plate. The number of colonies developing after overnight incubation was estimated and compared with the number obtained from a similarly inoculated control tube containing no penicillin, plated out immediately in order to assess the size of the original inoculum. Subcultures with less than half the numbers of colonies obtained from the control subcultures were considered to show inhibition and the first such tube in the range was taken as indicating the penicillin sensitivity of the strain.

The results showed that gravis strains of *C. diphtheriae* are rather more resistant than intermedius strains, and intermedius strains more so than mitis strains. Most of the strains tested required two or three times as much penicillin for *in vitro* inhibition as did the standard strain of staphylococcus which was inhibited by 0·1 unit of penicillin per ml. of medium.

In treating acute cases of diphtheria antitoxin was used as well as the following doses of penicillin: adults and children over 10 years, 60,000 units 4-hourly during the day only (240,000 units daily); children 5 to 10 years old, two-thirds of the above; children under 5 years, one-third of the above. Of 65 cases thus treated, 26 of 37 receiving a three-day course and 23 of 28 receiving a six-day course became free from the infecting organism within 4 days of the end of treatment. This compared favourably with previous rates of clearance published for cases

treated with antitoxin only, and also with results in a small control group of 22 cases, noted by the present authors, in which only 3 had the first of a series of consecutively negative swabs within a fortnight of admission to hospital.

The authors consider that it may be easier to prevent the appearance of a convalescent carrier than to cure the established carrier condition and they advocate that penicillin therapy should be begun as early in the disease as possible. *R. J. Lumsden*

See also Section Hygiene, Abstract 2112; Section Pharmacology, Abstract 2270; and Section Microbiology, Abstracts 2367–8. 2388.

2612. **Myocarditis and Pericarditis in Meningococcic Infections**

C. U. Lowe and L. K. Diamond. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **75**, 660–670, May, 1948. 4 figs., 23 refs.

This is the case report of a 13-year-old girl who developed pericarditis during the course of an acute meningococcal septicaemia with meningitis. Pericardiotomy revealed adhesions and fibrin only. The condition was interpreted as a meningococcal pericarditis modified by the previous administration of penicillin and sulphadiazine. Recovery was complete. *Douglas Gairdner*

2613. **Diagnosis of Brucellosis by Intravenous Injection of Vaccine.** (Brucelo-diagnostico intravenoso)

R. U. Dhaga del Castillo. *Archivos Peruanos de Patologia y Clinica* [*Arch. peruan. Patol. Clin.*] **2**, 389–408, Sept., 1948. Bibliography.

The clinical and laboratory diagnosis of brucellosis is difficult. In the present preliminary communication the author describes a method which he has found very serviceable—intravenous injection of heat-killed *Brucella melitensis*. The author used cultures of *Br. melitensis* only, but nevertheless in a patient from whom *Br. abortus* had been isolated by haemoculture the response was similar to that in 10 others infected with *Br. melitensis*. The dose recommended is 20 million organisms emulsified in 1 ml. saline, and the response is by rigor and rise in temperature, accompanied by headache, nausea and vomiting, coming on after 1½ to 5 hours. The temperature reaches its maximum within 12 hours and falls again within 32 hours. In some patients there may be a second rise, but to a lower degree and not accompanied by other symptoms. The reaction seemed to be tolerated better by patients in the chronic stages. The injection also caused liberation of agglutinins and opsonins [but no detailed figures of these are reported.] Injections were given to patients suffering from diseases other than brucellosis, such as tuberculosis, typhoid fever, dysentery, and rheumatic affections. These, without exception, failed to respond in the same way as did patients with brucellosis. The test thus reveals a " specific hypersensitivity ". The reaction is free from risk provided the dose is kept reasonably small. Fifty million organisms might cause a severe reaction. The question why this intravenous route is superior to others is discussed, but the conclusion that the signs of hypersensitivity are not produced by the latter methods of stimulation (as by vaccine therapy) is not very satisfying. *H. Harold Scott*

TUBERCULOSIS

2614. **A Rapid Mouse Test for Laboratory Diagnosis of Tuberculosis**

A. Milzer and E. R. Levine. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **69**, 16–17, Oct., 1948. 4 refs.

It has recently been shown that certain pigmented strains of mice are more susceptible to tuberculosis than are albino mice. Guinea-pigs are more susceptible when the bacilli are inoculated as a suspension in mucin solution. These two facts have been combined in developing a test for the rapid isolation of tubercle bacilli in mice. The bacilli were mixed with a 5% solution of mucin, and parallel tests were carried out with egg-yolk and saline. Approximately 500,000 organisms were injected into each animal; coloured mice of the C3H, dba, and C57 strains were used, and control experiments were carried out on CFW albino mice. Ten days after inoculation the animals were killed and examined for the presence of macroscopic lesions. These were observed in all of 18 mice of the C3H strain inoculated with tubercle bacilli mixed with mucin; of 18 mice given bacilli mixed with egg-yolk, 10 showed lesions, whereas there were no visible lesions in 16 mice of the same strain given bacilli suspended in saline. When CFW albino mice were used lesions were present in only 2 of 15 animals in which mucin had been employed, and in none of 12 animals given bacilli in saline. By this method, using mucin and pigmented mice, the authors were able to isolate tubercle bacilli from 14 patients. The material was prepared by standard methods, mixed with an equal volume of mucin solution, and inoculated both subcutaneously and intraperitoneally into 4 or 5 mice. In a footnote the authors state that the sensitivity of the test can be enhanced by feeding the mice on the cornmeal–gelatin–butter diet described by Dubos and Pierce. *D. J. Bauer*

2615. **Local Recrudescence as an Endogenous Source of Phthisis**

A. L. Woolf. *Tubercle* [*Tubercle, Lond.*] **29**, 221–230, Oct., 1948. 18 figs., 7 refs.

The author points out that, although the importance of superinfection is receiving increasing emphasis, the endogenous development of pulmonary tuberculosis must not be overlooked. Cases of endogenous development include those cases in which a primary or post-primary focus, after a long course with periods of activity and regression, constitutes a source for bronchogenic spread capable of producing active pulmonary tuberculosis. Four cases with post-mortem findings are recorded, in which local recrudescence of an old calcified focus was provoked by intercurrent disease in 3 of the

4 patients. The essential histological features were the coexistence of calcified foci with freshly liquefied areas, and the presence of enormous numbers of tubercle bacilli in the foci about to liquefy. *Maxwell Telling*

2616. **Closure and Healing of Tuberculous Cavities**
J. LOESCH. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 322–334, Sept., 1948. 12 figs., 1 ref.

The closure of pulmonary cavities is always a fascinating study. The observations on the five cases in this paper follow those given in a previous contribution and in all cases the closure of the individual cavity was brought about by its conversion to a caseous inspissated focus enveloped by a fibrotic capsule, the communication with one or more draining bronchi being obliterated. In 4 of the 5 cases in this second series, the cavities closed under therapeutic pneumothorax in 6 to 14 months, while in one case the cavity healed with rest in bed for 14 months. The 5 cases are described and illustrated by radiographs and photomicrographs. There was no difference in the mechanism causing disappearance of the thin-walled cavities and of thick-walled cavities of long standing, but the former closed much more quickly than the latter. An interesting observation is that under pneumothorax treatment, though the inspissated foci may shrink in the course of years, complete healing by replacement by a scar, formed by connective tissue growing in from the capsule with simultaneous absorption of the caseous material, probably takes place very rarely and only in small foci, if it occurs at all. The length of time of observation after disappearance of the cavities as judged radiographically was 6 years 8 months and 5 years respectively in the two cavities that closed by conversion to caseous foci, and from 3½ to 10 years in the 3 cases in which healing took place by scar tissue. The cavities were from 2 to 7·5 cm. in diameter. The mechanism of closure of the cavities treated by pneumothorax was by collapse, approximation, and final obliteration by connective tissue of the draining bronchial branches. [It is unfortunate that the healed scars and fibrous capsules were not examined for tubercle bacilli.]

Frederick Heaf

2617. **Monaldi Catheterization of Tuberculous Cavities. A Review of 34 Cases**
W. A. WILBUR. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 402–411, Oct., 1948. 1 fig., 5 refs.

The records are reviewed of 34 cases of pulmonary tuberculosis in which continuous suction drainage of tension cavities by the Monaldi method had been employed. Thoracoplasty had been performed in 11 after the cavity drainage had been stopped, and resulted in closure of the cavities in 9 cases; of these 2 patients remained sputum positive for tubercle bacilli. In none of 23 patients who did not undergo thoracoplasty was cavity closure obtained. Secondary infection of the catheter tract occurred in every case but was of little consequence; haemorrhage around or through the catheter occurred in 5 cases; broncho-pleural cutaneous fistulae developed in 4 cases after removal of the catheter. In 1 case an empyema developed after thoracoplasty. To minimize the risk of infection of the thoracoplasty wound from the infected catheter tract, anterior rib resection before thoracoplasty is advised. [This paper does not present a strong case for Monaldi drainage and its value would have been greater if the author had been reporting his own cases instead of a study of case records, some of which were incomplete.] *L. M. Franklin*

2618. **Bronchoscopy in Pulmonary Tuberculosis. A Study of Postbronchoscopic Increase of Disease**
E. O. COATES. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 412–420, Oct., 1948. 1 fig., 14 refs.

The records of 233 cases of pulmonary tuberculosis, in which 473 bronchoscopies had been performed, were examined and no radiological evidence was found of an undue liability for the disease to increase in the 2 months after bronchoscopy. A radiologist's report of increase of existing shadows or development of fresh ones was the only evidence of increase of disease considered; 15·4% of the bronchoscopies were followed by radiological evidence of increase of disease, and this percentage was no higher than the incidence of increase in the disease that had occurred in these cases in each of the three 2-month periods before bronchoscopy. No particular type of disease was found to be markedly liable to increase after bronchoscopy. *L. M. Franklin*

2619. **Anti-Tubercular Activity of Oxidation Products of Substituted *o*-Phenylene Diamines**
V. C. BARRY, J. G. BELTON, M. L. CONALTY, and D. TWOMEY. *Nature* [*Nature, Lond.*] **162**, 622–623, Oct. 16, 1948. 1 fig., 12 refs.

The study of tuberculostatic activity of substituted diphenyl ethers and related compounds, reported previously (see *Abstracts of World Medicine*, 1948, **4**, 214), has been extended to include diphenylamine derivatives. One of these, the base 2-aminodiphenylamine, when freshly dissolved in water, inhibited growth of *Mycobacterium smegmatis* at 1 in 100,000 dilution. When the solution was kept, and occasionally warmed, the inhibitory power increased gradually, reaching a figure of 1 in 1,000,000 at 5 weeks; at the same time the colour of the solution changed rapidly from pink to dark red. The responsible oxidation product proved to be a pigmented aromatic base (I), with the formula $C_{24}H_{18}N_4$, which inhibited *Myco. smegmatis* at 1 in 1,500,000 dilution and *Myco. tuberculosis* H37 Rv at 1 in 20,000,000; the activity was largely maintained in the presence of serum. Activity against other micro-organisms was not striking. The chemical aspects of the oxidation are discussed and the mechanism was studied by experiment. Further pigments were prepared by oxidation of variously substituted 2-aminodiphenylamines, but these were mostly less tuberculostatic than (I). Oral administration of (I) to guinea-pigs failed to control infection with the Ravenel Rv strain of *Myco. tuberculosis*; possibly the pigment was destroyed in the gut. Subcutaneous and intramuscular injections of the hydrochloride of (I) were

not practicable on account of severe local toxicity; intravenous injections in rabbits were rapidly fatal. Pigments derived from other substituted *o*-phenylene diamines are being prepared in the hope of finding lowered toxicity. Attention is drawn to the relation of these synthetic pigments to bacterial pigments that are phenazine derivatives—for example, pyocyanine and iodinin. *P. D'Arcy Hart*

2620. **Treatment of Tuberculosis with Sodium Tritionate. First Results.** (Tratamiento de la tuberculosis con el tritionato sódico. Primeros resultados)
T. Cerviá, R. Lluelmo, J. Sáez, and F. Chinea. *Gaceta Médica Española* [*Gac. méd. esp.*] **22**, 329–340, Sept., 1948. 5 refs.

Credit for the use of sulphur in tuberculosis is given to Xalabarder of Barcelona, who in 1926 stated that the beneficial results of gold therapy in tuberculosis were due to the sulphur ion in the gold thiosulphate complex. In 1946 Xalabarder published his results with a Spanish product, consisting of 2·5% sodium tritionate stabilized in a thiosulphate-sulphite system. It contains 40·3% sulphur and is known as "tri-om" commercially. It diffuses rapidly and weakens the acid fastness of the bacilli in suspension but has little effect on cultures, although it diminishes their pathogenicity. It has desensitizing properties in experimental tuberculin shock, and experiments with indian ink have shown its stimulating properties on the reticulo-endothelial system. In experimental tuberculosis it has some curative effect. It has a wide therapeutic margin of safety, the body eliminating 40 to 50% of the compound in the urine.

Infiltrative lesions before the productive or caseous stage has been reached appear to be most favourably influenced. When the lesions are chiefly productive the results are not so obvious and prolonged treatment is required. The authors cite Blajot's conclusions (*Med. clín.*, 1947, **5**, 217) as follows: (*a*) the results are as good as the best obtained with chrysotherapy; (*b*) early lesions regress with great rapidity; (*c*) the effect can be assessed within a short period of time; (*d*) sulphur therapy is at best only an adjuvant and should not supersede the established methods of treatment. The authors discuss their results in 48 cases of pulmonary tuberculosis treated with tri-om. The following table summarizes the results obtained.

	Cured	Improved	No Change	Worse	Treatment Suspended	Total
Early types ..	4	5	1	0	2	12
Exacerbation foci	4	1	1	0	1	7
Haematogenous T.B. ..	0	4	3	2	1	10
Ulcero-caseous	0	1	5	0	1	7
Fibro-caseous	0	0	8	1	2	11
Productive types	0	0	1	0	0	1
Totals . ..	8	11	19	3	7	48

Two methods of administration were adopted; in the first, injections of 10 ml. were given intravenously daily, and in the second, injections were given every 3 or 4 days. As the first method was used for early cases, superior results were obtained. In 7 cases the treatment had to be suspended because of haemoptysis (5 cases), general reaction (1 case), or nocturnal dyspnoea (1 case). *J. J. Giraldi*

2621. **The Passage of Streptomycin from Blood to Cerebrospinal Fluid. Interim Results of Treatment of Tuberculous Meningitis with Streptomycin.** (Om Overgangen af Streptomycin fra Blod til Spinalvaedske)
H. C. A. Lassen and K. A. Jensen. *Ugeskrift for Læger* [*Ugeskr. Læg.*] **110**, 1069–1080, Sept. 16, 1948. 5 figs., 7 refs.

The evidence available about the nature of the blood-brain barrier is first reviewed, and it is pointed out that the barrier, normally impermeable to sulphonamides, may become permeable when the meninges are inflamed, so that intrathecal administration of these compounds becomes necessary. The blood-brain barrier has been considered impermeable to streptomycin, but experiments carried out by the authors show that this is not the case. The streptomycin content of blood and of cerebrospinal fluid was simultaneously determined in patients receiving streptomycin by intramuscular injection only. Curves obtained from 4 cases of tuberculous meningitis are presented, showing that streptomycin is present in the cerebrospinal fluid, although the concentration is lower than it is in the blood. In early cases of the disease when patients were receiving up to 100 mg. per kilo of body weight daily by intramuscular injection, the amount of streptomycin present in the cerebrospinal fluid was 10 to 30 times higher than the *in vitro* lethal concentration for tubercle bacilli; this level could be maintained by two injections in each 24-hour period. A control investigation was carried out in patients suffering from conditions other than meningitis who were receiving streptomycin intramuscularly; no streptomycin was found in the cerebrospinal fluid. In 5 patients with *Haemophilus influenzae* meningitis the cerebrospinal fluid contained appreciable amounts of streptomycin.

In all 15 cases of tuberculous meningitis were treated with streptomycin; 8 of the patients died, 6 shortly after beginning treatment, and 2 after 7 to 8 months; 4 were apparently cured, and in the remaining 3 the prognosis was doubtful. *D. J. Bauer*

2622. **Results of Treatment of 85 Cases of Tuberculous Pharyngo-laryngitis with Streptomycin.** (Résultats du traitement de 85 cas de pharyngo-laryngites tuberculeuses par la streptomycine)
G. Arnaud. *Acta Oto-Rhino-Laryngologica Belgica* [*Acta oto-rhino-laryng. belg.*] **2**, 3–16, 1948.

The author studied 85 cases of tuberculous pharyngo-laryngitis at the tuberculosis clinic of the Laënnec Hospital, Paris, during 1947; 67 patients received streptomycin intramuscularly and 18 by aerosol. The effect of intramuscular treatment was analysed.

Dysphagia, present in 62 out of the 67 cases, disappeared in all but one case after 5 to 20 days of treat-

ment. Dysphonia or aphonia was present in 52 cases; in 26 the voice became normal, in 20 it improved, and in 6 it remained unchanged. In 23 cases lesions were clinically cured, in 33 improved, and in 6 unchanged; in 5 cases they became worse. Lesions of the granular and "infiltrating oedematous" type responded better than did those of the ulcerating or vegetative type. Lesions of the pharynx healed in 20 to 50 days while those of the larynx healed in 40 to 80 days. Pharyngo-laryngeal tuberculosis responded in 35 to 100 days. The pharynx always healed first. As regards the underlying lung disease, best results were obtained in miliary tuberculosis, while the caseating nodular forms were less favourable and cavitary forms the least favourable. Many of the patients with favourable response of pharyngo-laryngeal lesions still had tubercle bacilli in their sputum. Even among the 56 cases in which the effect on the upper respiratory lesions was favourable, there was corresponding improvement in the lung disease in only 21. As the pharyngeal lesions healed, they were replaced by normal, healthy looking mucosa. In the region of the larynx healing by scar tissue accompanied by deformities was more typical, and cicatricial stenosis of the glottis was sometimes met with.

A daily dose of 1 to 1·5 g. (rarely 2 g.) streptomycin was used for a variable length of time. Some cases responded to a relatively short course (25 g.) while others needed 150 to 300 g. Only one case of adverse effect of streptomycin was seen among 350 cases. [Apart from this, impairment of vestibular or cochlear function was not noticed.] Eighteen patients were treated by streptomycin aerosol with poor results. While the symptoms were ameliorated in some cases, there was little effect on the lesions and many patients could not tolerate this form of treatment.

In conclusion it is pointed out that while streptomycin is invaluable in treating the upper respiratory lesions, the pulmonary disease needs appropriate medical treatment. Success depends more than ever on the closest collaboration between physician and laryngologist.

J. Kodíček

2623. **The Use of Streptomycin in Tuberculous Tracheo-bronchitis**
J. J. O'KEEFE. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol., etc., St Louis*] **57**, 784–790, Sept., 1948. 2 figs., 5 refs.

Attention is drawn to the promising results so far reported of streptomycin in tuberculous tracheo-bronchitis. Histamine-like reactions are probably due to impurities and are becoming less common. Sensitization symptoms are not infrequent. Involvement of the cochlea and labyrinth is the most distressing toxic manifestation.

In the present series 62 patients with tuberculous tracheo-bronchitis were selected for treatment on account of either "bronchoscopic evidence of mucosal disease as manifested by persistent ulcerations, granulations and stenoses; or "roentgen signs of obstructive phenomena as seen in atelectasis or in the ballooning of cavities following collapse measures". Sanatorium regimen and collapse therapy were not interrupted. Eleven patients received streptomycin by aerosol alone, 15 by concomitant aerosol and parenteral administration, and 36 by parenteral administration alone. The aerosol was given as 50 mg. of the drug in 1 ml. of sterile isotonic saline every 2 hours to a total daily dosage of 500 mg. Parenterally the dose was 500 mg. intramuscularly twice daily. Larger doses were used intramuscularly at first but were abandoned because of untoward reactions [nature not stated]. All cases showed signs of severe and long-standing activity or had failed to respond to conventional forms of management. Combined aerosol and intramuscular administration gave better results than did administration by either route alone; frequently healing of ulcers of the tracheo-bronchial mucosa and disappearance of granulations were observed within 4 to 6 weeks. Of 34 such cases treated parenterally either with or without aerosol administration 18 were classed as healed, 12 improved, and 4 unimproved. Where there were obstructive lesions these resolved sufficiently to permit re-expansion in all cases of atelectasis and eventual effective collapse in the case of large centres. *Norman W. MacKeith*

2624. **Streptomycin in Preparation for Collapse Therapy**
J. D. STEELE and T. R. MURPHY. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 393–401, Oct., 1948. 3 figs., 9 refs.

Twelve cases of pulmonary tuberculosis treated by thoracoplasty, 3 by artificial pneumothorax, and 2 by extrapleural pneumolysis are reviewed. These were cases mainly of exudative disease, which was progressive in 13 cases. Streptomycin was given to all patients for periods of from 44 to 140 days (average 79) before starting collapse therapy, and administration was continued until collapse therapy was fully established. The length of the course of streptomycin varied from 80 to 211 days (average 162); 0·75 to 2 g. was given daily (usually 1 g.) in three doses. The radiological appearances in each case are reproduced diagrammatically and all show a satisfactory outcome, but no final assessment is attempted because of the short follow-up period. It is thought that without streptomycin treatment most of the patients would never have become fit for consideration for collapse therapy. *L. M. Franklin*

2625. **Determination of Streptomycin Sensitivity of Tubercle Bacilli by Use of Egg-yolk Agar Medium**
A. G. KARLSON and G. M. NEEDHAM. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **23**, 401–408, Sept. 1, 1948. 2 figs., 7 refs.

Preparation of Herrold's medium is first described in detail. Briefly, nutrient agar containing 2% of glycerin is first put up in 120-ml. lots. When the medium is to be prepared the glycerin agar is melted and cooled, and to each lot is added the requisite amount of streptomycin in 1 ml. of distilled water. Immediately after the streptomycin has been added the yolk of a fresh egg is poured directly into each lot, the bottle inverted several times to mix, and the mixture poured into tubes and slanted.

Streptomycin concentrations used by the authors were 1, 10, 50, and 100 μg. per ml. of medium.

As regards the bacterial inoculum in the sensitivity test, the authors state that tests may be done by inoculating sputum or other material on the medium without making a preliminary isolation, provided that the specimen is heavily laden with tubercle bacilli and the bacilli are uniformly distributed in it. They add, however, that, in their experience, most specimens have too few tubercle bacilli to permit the direct test, and this is especially true of specimens from streptomycin-treated patients. In most cases, therefore, a preliminary isolation has to be made, and sensitivity tests must be done on pure cultures. Several methods are suggested.

1. If the culture to be tested consists of moist growth which breaks up easily, it may be possible to inoculate the tubes with a loop, but the tubes must be inoculated with approximately equal amounts of growth, free from large clumps that might be mistaken for colonies later on, and the inoculum must be spread evenly over the surface of the slant.
2. A suspension may be prepared by grinding up a few flakes of growth and adding liquid medium, or 0·01 molar phosphate buffer; each tube is inoculated with 0·1 ml. of suspension. Suspensions should be about equivalent to tube No. 1 of the McFarland nephelometer, but this density is not critical, and may vary within a tenfold limit without affecting the end-point.
3. Several colonies are transferred to 2·5 ml. of liquid Dubos medium and incubated for 48 to 96 hours. If the tube is agitated daily for 2 to 5 minutes sufficient growth will usually have occurred in the above time. Turbidity is adjusted either by dilution or by further incubation, and should correspond approximately to McFarland nephelometer tube No. 1, but this is not critical. Each tube of egg-yolk medium is inoculated with 0·1 ml. of liquid culture.

The test is usually read after 14 days' incubation, and experiments show that the streptomycin in the medium remains stable throughout this time. Of 149 cultures from patients who had received no streptomycin, all were resistant to only 1 μg. or less of streptomycin per ml. of medium. It was found that 245 strains of tubercle bacilli from clinical material had the same sensitivity to streptomycin on the egg-yolk agar as in Proskauer and Beck's liquid medium. Among advantages claimed by the authors for the method are: ease of preparation of the medium; greater ease in reading differences of growth in a solid medium; the fact that cultures, particularly those which have been stored for a long time, which fail to grow in a liquid medium may grow on the egg-yolk agar; that individual colonies may be selected from solid medium for further study. *T. D. M. Martin*

2626. **Enhancement of Growth of a Strain of *M. tuberculosis* (var. *hominis*) by Streptomycin**
G. A. Spendlove, M. M. Cummings, W. B. Fackler, and M. Michael. *Public Health Reports, Washington* [*Publ. Hlth Rep., Wash.*] **63**, 1177–1179, Sept. 3, 1948. 6 refs.

During the routine testing of a strain of *Mycobacterium tuberculosis* derived from the sputum of a patient with pulmonary tuberculosis who had been receiving streptomycin for 96 days, it was noted that growth was poor in the control tube while it was abundant in all tubes containing streptomycin in concentrations of 1, 5, 10, 100, and 1,000 μg. per ml. The phenomenon was noted in Dubos liquid medium and on Loewenstein–Jensen medium. After the second transfer of this strain on Dubos medium with graded amounts of streptomycin, the authors were successful in reproducing their findings in 5 of 7 trials. The cause of the discrepancy is not understood, but two possibilities are suggested: (*a*) the culture is a mixture of strains, or (*b*) unknown variables, such as differences in lots of culture media and streptomycin, may have altered the finding. They conclude that this strain shows partial dependence on streptomycin for growth, and have isolated a second strain from the same patient, three months after conclusion of streptomycin treatment, which showed the same characteristic. Streptomycin-sensitivity of a culture isolated from this patient before streptomycin therapy was begun was not tested. Clinically, it appeared that the patient's condition deteriorated during the second half of the period of streptomycin therapy. *T. D. M. Martin*

See also Section Microbiology, Abstract 2378.

2627. **The Significance of Positive Cultures in Apparently Adequately Treated Patients with Pulmonary Tuberculosis**
H. Abeles. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 308–313, Sept., 1948. 4 refs.

A survey was made of patients discharged from a sanatorium with arrested tuberculosis, and a few tubercle bacilli in their sputum or in gastric culture, to determine whether discharge had been justified by the subsequent history. A total of 199 patients were followed up for about 4 years. Before their discharge concentrated specimens of sputum and cultures of sputum and gastric washings were examined at least once a month for 6 months. From 104 patients cultures of sputum and/or gastric juice were negative and from 95 were occasionally positive. The follow-up study showed that 36 of the 199 patients had had to be readmitted to the sanatorium because of reactivation of the disease; the largest number of readmissions occurred within 2 years of the patient's being discharged. *Franz Heimann*

2628. **The Role of the " Wax " of the Tubercle Bacillus in Establishing Delayed Hypersensitivity. I. Hypersensitivity to a Simple Chemical Substance, Picryl Chloride**
S. Raffel and J. E. Forney. *Journal of Experimental Medicine* [*J. exp. Med.*] **88**, 485–501, Oct. 1, 1948. 1 fig., 35 refs.

In this study the previously acquired knowledge of the directive properties of " purified wax " of the tubercle bacillus in evoking the delayed type of allergy was applied, the purified wax fraction being combined with an artificial [protein-type] antigen, picryl chloride. This simple chemical substance has been known for some time to possess many of the antigenic properties of natural proteins.

As expected typical allergy of the delayed type to old tuberculin could be induced in guinea-pigs after one intraperitoneal injection of picryl chloride together with

purified wax—control animals treated with picryl chloride alone through the skin, intradermally, subcutaneously, and intraperitoneally as well as with picryl chloride in water-in-oil emulsion intraperitoneally showed no such response. Certain difficulties were caused by skin irritations due to picryl chloride. Irritation, however, disappeared before the maximum reaction to old tuberculin could develop. By prolonged observation and careful measurements of the skin reactions the results could be properly assessed. Delayed allergy induced by picryl chloride and purified wax conformed to the pattern of allergy induced by tuberculoprotein plus purified wax, that is, it was unrelated to common anaphylactic reactions and could not be transferred passively to normal guinea-pigs. The directive role of wax is only evident when it is injected into or near the same site as the protein type of antigen.

Because, after application of the substance through the skin, delayed contact reactivity to picryl chloride or other simple chemical substances may sometimes occur the author discusses the possibility of the presence as a cellular component of the skin of a lipid with properties similar to those of tubercle bacillary wax.

[Technical details should be read in the original.]

K. S. Zinnemann

2629. **The Effect of Nicotinic Acid Amide on Experimental Tuberculosis of White Mice**

D. McKENZIE, L. MALONE, S. KUSHNER, J. J. OLESON, and Y. SUBBAROW. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1249–1253, Oct., 1948. 5 refs.

Thirty derivatives of nicotinic acid were tested for anti-tuberculous action in mice. The technique was to infect intravenously Swiss mice, 17 to 20 g. in weight, with 0·25 mg. of a 14- to 18-day culture of H37 Rv, a procedure which usually killed untreated animals in 3 to 3½ weeks, giving lesions mainly in the lungs. The drugs were mixed in the diet, at up to maximum tolerated percentage, from the day after infection onwards; activity was estimated on the basis of weight loss, percentage survival, and lung involvement after 3 weeks. The most active compound was found to be nicotinamide, which, at 0·75% in the diet, was markedly suppressive to the spread of tuberculosis, being roughly equivalent in activity to 4 mg. streptomycin daily subcutaneously.

P. D'Arcy Hart

2630. **Study of Skin Tests with Tuberculin in Miliary Tuberculosis of Adults.** (Étude des tests cutanés à la tuberculine dans les tuberculoses miliaires de l'adulte)

E. BERNARD, B. KREIS, A. LOTTE, and G. FOSSÉ. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **64**, 1011–1016, Oct. 29, 1948. 1 ref.

Tuberculin tests were carried out on 95 adult patients with miliary tuberculosis, the diagnosis having been confirmed in all cases. The percutaneous reaction was negative in 37. In parallel tests on an unselected group of patients with non-miliary pulmonary tuberculosis there were no negative results; in a comparable group of gravely ill patients there were 11 tuberculin-negative cases. Quantitative intradermal tests in the three groups yielded essentially similar results. In the miliary group there were 51 in poor general condition; 26 of these were negative to the percutaneous tests and 7 did not react to 1 mg. of tuberculin intradermally. Of 18 in good general condition 3 were negative to percutaneous tests and all reacted to 1 mg. of tuberculin; 11 (61%) were positive down to 0·1 mg. This is compared with 4% positive down to 0·1 mg. in the unselected non-miliary group. It would appear that the disparity between the three groups cannot be accounted for wholly by differences in the general condition of the patients. In those patients who responded well to streptomycin there was, in general, an increase in the level of tuberculin sensitivity at the end of the 3 to 4 months' treatment; that of the group which failed to respond tended to remain stationary. The level of the tuberculin sensitivity before treatment appeared to have no prognostic significance.

J. R. Bignall

2631. **Public Health Significance of Rare Tubercle Bacilli in Sputum**

F. M. POTTENGER. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **58**, 314–321, Sept., 1948. 9 refs.

The infectivity of tuberculosis is an important but highly controversial subject. It is easy to make dogmatic statements when our present knowledge of the pathogenesis of tuberculosis prevents adequate proof. In this interesting paper the subject is introduced by the observation that by using the dilution–flotation–picric-acid technique and examining three-day specimens of sputum every 6 weeks it has not been possible to demonstrate an absence of tubercle bacilli for three consecutive examinations in more than 4 or 5% of patients at the Pottenger Sanatorium at the time of their discharge. This so-called " rare bacillus " stage of tuberculosis is compared with the acute stage when many millions of bacilli are expectorated every day. The danger from contact with such infection is considered to be influenced by the susceptibility of the host and the environment in which exposed persons are nurtured. A plea is made for a more rational attitude toward primary infection and a better appreciation of its protective nature but with the realization of the risk that endogenous metastases may arise from it. Vaccination is advocated to protect the highly susceptible, both those in contact with " rare bacilli " cases and those exposed to massive infection.

Frederick Heaf

2632. **Primary Tuberculosis with Meningism and Bacilli in the Spinal Fluid**

K. CHOREMIS and G. VRACHNOS. *Lancet* [*Lancet*] **2**, 408–409, Sept. 11, 1948.

The authors report two cases in which there were signs of meningism and tubercle bacilli were present in the cerebrospinal fluid but tuberculous meningitis did not develop. The first case was of a boy aged 11 months who developed a cough, anorexia, fever, and restlessness 1 month after bronchopneumonia and entero-colitis.

The Mantoux reaction was strongly positive in a dilution of 1 in 10,000 whilst the cerebrospinal fluid (cisternal puncture under normal pressure) contained 20 mg. protein, 40 to 50 mg. glucose, and 540 mg. chlorides per 100 ml., 8 cells per c.mm., and tubercle bacilli on culture. The second was in a boy aged 2 years, contact of a case of pulmonary tuberculosis. The Mantoux reaction was positive in a dilution of 1 in 1,000 and the cerebrospinal fluid (pressure slightly increased) contained 20 mg. protein per 100 ml., 1 to 2 cells per c.mm., and tubercle bacilli on culture. In this case streptomycin was given. Both patients recovered without the development of meningitis, the first in 4 and the second in 2½ months. The authors put forward two explanations for the presence of tubercle bacilli in the cerebrospinal fluid: (1) that bacilli may be present without any focal lesion in the brain or meninges; or (2) that they may derive from a minimal meningeal lesion which resolves. They consider the second explanation the more likely, and suggest that in assessing the " cure " of tuberculous meningitis greater weight should be attached to chemical and cytological findings in the cerebrospinal fluid than to the results of culture for the tubercle bacillus.

S. Roodhouse Gloyne

See also Section Hygiene, Abstracts 2207, 2219.

YAWS

2633. **Penicillin Therapy of Yaws and Serologic Results**
C. R. REIN, T. H. STERNBERG, J. H. DWINELLE, and A. J. SHELDON. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph., Chicago*] **57**, 942–952, June, 1948. 18 refs.

Penicillin has given excellent clinical results in yaws and is regarded as the treatment of choice in this so-called syphiloid infection. After penicillin the serum of patients with yaws takes longer to become negative than the serum of patients with early syphilis, and this paper describes a serological study of 500 cases observed for 12 months. Only 15% of 477 patients were serum-negative twelve months after treatment, though the titre was reduced in over 90%. Factors influencing the fall in titre and the serological response are discussed. One of the most significant of these factors is the duration of infection before the start of treatment; this is usually longer in yaws than in early syphilis: hence the longer interval before the patient becomes serum-negative.

S. M. Laird

PROTOZOAL INFECTIONS

2634. **Resistance to Sulphadiazine and " Paludrine " in the Malaria Parasite of the Fowl (*P. gallinaceum*)**
A. BISHOP and E. W. MCCONNACHIE. *Nature* [*Nature, Lond.*] **162**, 541–543, Oct. 2, 1948. 8 refs.

The authors increased the resistance of *Plasmodium gallinaceum* to sulphadiazine by methods similar to those used with proguanil (" paludrine ") [see *Abstracts of World Medicine*, 1949, **5**, 253]. In about 12 months the resistance was so much increased that the parasites grew in chicks receiving a dose of 20 mg. per 20 g. of body weight twice daily on consecutive days, the minimum dosage which adversely affected the growth of the normal strain being 0·625 mg. per 20 g. similarly given; this is a thirty-two-fold increase.

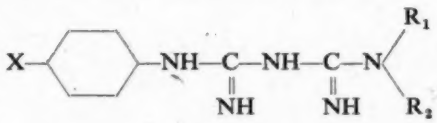
The sulphadiazine-resistant strain produced less intense infections in untreated chicks than the parent strain. Exoerythrocytic schizonts were present during treatment of the resistant strain with sulphadiazine. This strain was resistant to sulphathiazole, sulphanilamide, and sulphapyridine and also resisted proguanil given in a dose of 0·1 mg. per 20 g. twice daily, which will suppress the normal strain of *P. gallinaceum*. Two other strains, made resistant to 5 mg. per 20 g. of sulphadiazine, were also resistant to 0·5 mg. per 20 g. of proguanil. A proguanil-resistant strain was tested with 1·25 mg. per 20 g. of sulphadiazine and found to be resistant; higher doses were not tried. The authors think that while resistance to proguanil developed simultaneously with resistance to sulphadiazine in the parasites exposed to the latter drug, the converse probably did not occur, resistance to sulphadiazine developing only after prolonged treatment with proguanil; this point is being further investigated. *para*-Aminobenzoic acid inhibits the action of sulphonamides on *P. gallinaceum* but not apparently that of proguanil.

P. gallinaceum, made resistant to 5 mg. per 20 g. of sulphadiazine twice daily retained the whole resistance after two consecutive passages through *Aëdes aegypti*.

J. F. Corson

2635. **Studies on Synthetic Antimalarial Drugs. XX. The Blood Concentrations and Physiological Distribution of Some Homologues of Paludrine in Relation to their Antimalarial Activities**
A. SPINKS. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **42**, 190–197, Sept., 1948. 17 refs.

Arylbiguanides of the general formula



were the most active of new antimalarials studied by Curd, Davey, and Rose (*Amer. trop. Med. Parasit.*, 1945, **39**, 208), and of these " No. 4430 " and " paludrine " (proguanil) were especially effective in human malaria; in 4430, X=Cl, R_1=CH_3, and R_2=*iso*-C_3H_7, and proguanil differs only in that R_1=H. Homologues of proguanil (X=Cl) varied greatly in antimalarial activity, some being quite inactive even in large doses.

The factors concerned in the mode of action of the drugs may be roughly divided into those affecting intrinsic activty and those affecting access of the drug to the parasite (absorption, distribution, degradation, and excretion of the drug and its affinity for the parasite),

The authors compared the blood, plasma, and tissue concentrations of some homologues with those of proguanil; the blood and plasma concentrations indicate the difference between the rate of absorption and the rate of removal (degradation and excretion) of the drug, while the tissue distribution shows the affinity of the drug for cellular structures. The determinations were made in the rat, rabbit, and chick; these are described, and are shown in detail in tables.

In the chick and rat the compounds of lower molecular weight gave higher blood concentrations; this probably depends mainly on the rate of absorption, though the rate of disappearance from the blood would also be a factor. The rate of metabolism of proguanil analogues is an important factor in their rates of disappearance from the blood. In these experiments the compounds differed little in rate of disappearance from the blood and in distribution in the tissues. Rats received doses of 80 mg. per kilo and chicks 40 mg. per kilo; the tables show that concentrations in blood, plasma, and some tissues of proguanil and 4565 (both active) were higher in the chick, while concentrations of the inactive drug 5093 were higher in the rat. The authors suggest that the inactivity of 5093 is due to low intrinsic activity or to faulty metabolism. Therapeutic effects may depend on association of blood and plasma concentration with intrinsic activity. *J. F. Corson*

2636. **Synergistic Effect of Chlorguanide and Sulfadiazine against *Plasmodium gallinaceum* in the Chick**
J. GREENBERG, B. L. BOYD, and E. S. JOSEPHSON. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **94**, 60–94, Sept., 1948. 7 refs.

In tests for activity against *Plasmodium gallinaceum*, a drug is given by mouth to 1-week-old chicks twice daily for 4 days, beginning 4 to 5 hours before subcutaneous inoculation of sporozoites or intravenous injection of erythrocytes containing parasites. The drug is said to be active against sporozoite-induced malaria when at least half of the birds show no infection during 35 days after inoculation (complete protection) or when parasitaemia is delayed in at least half of the birds (partial protection); in blood-induced malaria the minimum effective dose (M.E.D.) is that which causes a 75% reduction in the mean parasitaemia as compared with untreated controls.

The authors tested sulphadiazine and " chlorguanide " (proguanil) separately and together in infections of chicks with strain A of *P. gallinaceum*; the experiments were made at the National Institute of Health, Bethesda, Maryland. Against sporozoite-induced infection sulphadiazine alone in a dosage of 0·5 mg. per g. of body weight twice a day protected less than half of the birds, and proguanil alone in a dosage of 0·03 mg. per g. twice daily (the maximum tolerated dose) delayed the onset of parasitaemia but protected very few birds completely; toxic doses (0·06 mg. per g.) of proguanil, however, completely protected 5 of 9 birds. When given together, much smaller doses gave complete protection; 0·0078 mg. per g. twice daily of sulphadiazine and 0·015 mg. per g. twice daily of proguanil completely protected 7 of 10 birds, and in the other 3 birds parasitaemia was delayed. The smallest completely protective dose of the combination is expressed as $\frac{C}{4}+\frac{S}{64+}$, where C is that of proguanil alone and S that of sulphadiazine alone. In blood-induced infections the M.E.D. of sulphadiazine alone was 0·03 mg. per g. twice daily and that of proguanil 0·001 mg. per g. twice daily; in combination the M.E.D. was $\frac{C}{8}+\frac{S}{4}$ or $\frac{C}{4}+\frac{S}{32}$ [in the table it is $\frac{S}{16}$ or 0·00185 mg. per g. twice daily].

In the combined treatment the toxicities of the drugs were added. When the drugs were given together to uninfected chicks the plasma levels of sulphadiazine were raised by from 33 to 100%, while the levels of proguanil were unaffected; the experiments show, however, that this does not account for the increased protection given by the combination. The authors suggest that similar effects may be produced in human malaria and in bacterial infections. *J. F. Corson*

2637. **The Inhibition of the Anti-trypanosomal Activity of Arsenoso Compounds and Acridines by Esters and Amides of Organic Acids**
W. L. SCHLEYER and R. J SCHNITZER. *Journal of Immunology* [*J. Immunol.*] **60**, 265–276, Oct., 1948. 21 refs.

The esters and amides of benzoic, *p*-hydroxybenzoic, and *p*-aminobenzoic acids antagonize *in vitro* the immobilization of *Trypanosoma equiperdum* by " maparside " (oxophenarsine hydrochloride). Another arsenoso compound " Nu 1067 " (N-*p*-arsenosobenzyl-glycine amide hydrochloride) is similarly inhibited by the esters and amides of *p*-hydroxybenzoic acid, 2-5-dihydroxybenzoic acid, 2-4-dihydroxybenzoic acid, and nicotinic acid. Acriflavine is inhibited by the esters and amides of *p*-hydroxybenzoic and nicotinic acids. In all instances the acids themselves are ineffective. The antagonism between methyl-*p*-hydroxybenzoic acid and mapharside or acriflavine can also be demonstrated *in vivo*. The only information bearing on these observations that has been obtained so far is that methyl-*p*-hydroxybenzoate interferes with the inhibition of *Bacterium coli* oxidases by arsenoso compounds. *C. L. Oakley*

2638. **Diodoquin Compared with E.B.I. and Chiniofon in the Early Treatment of Amoebic Dysentery in Burma**
R. W. PARNELL. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **51**, 200–202, Oct., 1948. 2 refs.

This paper deals with two series, each of 34 cases of amoebic dysentery in R.A.F. personnel. Choice of alternate cases was impracticable on account of irregular drug supply, but other factors such as length of stay in the war area and associated bacillary infection were comparable in the two series. Follow-up study comprised clinical examination, sigmoidoscopy, and three examinations of faeces for motile amoebae made one month after the end of treatment. This was repeated a month later

in about one-third of the cases (the author admits that this period was too short for a final assessment of cure). Each group received 6 injections of 1 gr. (65 mg.) emetine and 100 g. sulphaguanidine also in the first week, followed in group I by 12 daily doses of 3 gr. (0·2 g.) emetine bismuth iodide and 10 daily retention enemata of 2·5% chiniofon, and in group II by 3 tablets of diodoquin 3 times daily for 20 days (daily dose 9·6 gr.). The cure rate was 71% in group I and 74% in group II. These results confirm the opinion of Wright and Coombes, who reviewed results in army personnel in India. The final conclusion is that diodoquin orally is as effective as chiniofon rectally and is preferred by both patients and staff. *Clement Chesterman*

2639. **Biological Properties of a Strain of Toxoplasma Recovered from a Fatal Case of Congenital Toxoplasmosis**
I. RUCHMAN and R. J. JOHANSMANN. *American Journal of Tropical Medicine* [*Amer. J. trop. Med.*] **28**, 687–695, Sept., 1948. 4 figs., 13 refs.

The authors record observations on the biological and immunological properties of a strain of toxoplasma recovered from a case of congenital toxoplasmosis in an infant who died in a Cincinnati hospital at the age of 37 days as the result of the infection. On post-mortem examination parasites, stained by Wright's method, were seen in smears of the brain. The parents and two siblings of the infant were apparently healthy, but sera taken from all of them, except one of the siblings, contained toxoplasma-neutralizing antibodies. Tissues were removed aseptically from the patient and ground in saline to make a 10% suspension, which was injected intracerebrally and intraperitoneally into mice and guinea-pigs. The presence of toxoplasma was demonstrated in all the animals inoculated with material from the brain, and presumptive evidence was obtained of their presence in the spleen, but there was no sign of parasites in the liver.

This strain of toxoplasma (C.G.), which was kept by passages through mice, proved to be pathogenic for the guinea-pig, rabbit, hamster, cotton-rat, and white rat, and to a lesser degree for chicks. In every case the presence of the parasites in the brain of the experimental animals was demonstrated in stained smears. The immunological properties of strain C.G. were investigated by cross-immunity and cross-neutralization tests with a known virulent R.H. strain of toxoplasma. Mice, rabbits, and guinea-pigs which had recovered from infections with C.G. strain were inoculated with R.H. strain: all of them failed to acquire an infection with the latter. Cross-neutralization tests were carried out with suspensions of toxoplasma-infected mouse brain on the one hand, and sera from members of the family of the C.G. patient, serum of a monkey immunized with R.H. strain, and serum from another patient (R.B.) with congenital toxoplasmosis, on the other. Good cross-neutralization was demonstrated between all the strains.

In view of the morphological similarity of all toxoplasma, and of their wide host range and immunological identity, it is concluded that there is only one species of toxoplasma. *C. A. Hoare*

FUNGUS INFECTIONS

2640. **Histoplasmosis in Wild Rats. Occurrence and Histopathology**
C. W. EMMONS and L. L. ASHBURN. *Public Health Reports* [*Publ. Hlth Rep., Wash.*] **63**, 1416–1422, Oct. 29, 1948. 2 figs., 6 refs.

Typical strains of *Histoplasma capsulatum* have been isolated from 16 feral rats (*Rattus norvegicus*) and one mouse (*Mus musculus*) trapped in Loudoun County, Virginia. No association was observed between these rodent cases and the previously reported human cases of the disease in this area. The microscopical lesions were small epithelioid granulomata in which fungi were generally few in number. Histoplasma was found also in monocytes outside the lesions. It is suggested that the frequent occurrence of *H. capsulatum* in the common brown rat may be important in the endemicity of histoplasmosis in many widely separated areas of the world. The data suggest that *H. muris* should be reduced to synonymy.—[Authors' summary.]

2641. **The Use of Yeast Phase Antigens in a Complement Fixation Test for Histoplasmosis. II. Results with Ground Antigens**
C. C. CAMPBELL and S. SASLAW. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1207–1211, Oct., 1948. 6 refs.

The authors have prepared a new and more stable antigen for use in the complement-fixation test for the diagnosis of histoplasmosis. Five-day cultures of *Histoplasma capsulatum* and *Blastomyces dermatitidis* on glucose-cystine agar, containing penicillin and streptomycin, are washed off with sterile buffered saline, filtered through sterile gauze, centrifuged, and resuspended in sterile buffered saline containing 1 in 10,000 " merthiolate ". The product is stored at 37° C. for 7 days, again centrifuged, and the sediment ground up with a little sterile buffered saline. The clear supernatant fluid is used as an antigen, merthiolate being added as a preservative.

Results have shown that there is no anti-complementary activity or loss in titre after storage in the refrigerator for 12 weeks. Cross reactions will occur with *Histoplasma* and *Blastomyces dermatitidis*, which have a common antigen, but none was demonstrated with *Candida albicans*, *Sporotrichum schenckii*, or *Blastomyces brasiliensis*. *E. T. Ruston*

TRICHINIASIS

2642. **The Origin of Latent Cases of Trichiniasis.** (Zur Entstehung latenter Trichinosefälle)
H. WENDEROTH. *Zentralblatt für Bakteriologie, Parasitenkunde u. Infektionskrankheiten, Abteilung* 1, *Originale* [*Zbl. Bakt.*, 1. *Abt. Orig.*] **152**, 590–599, 1948. 53 refs.

The factors influencing the degree and (clinical) severity of trichiniasis, as recorded in the available literature, are reviewed. These are classified as parasite

factors (massiveness of infection, age of parasites, diminution of viability of parasites caused by unfavourable environmental influences, and property of the capsule surrounding the parasites) and host factors (species, susceptibility, age of the host, size of muscular tissue particles containing the encapsulated parasites, action of digestive juices, rate of passage through the intestinal tract, immunity to parasitic invasion, and simultaneous existence of any other disease). A brief description is given of an outbreak of trichiniasis involving about 150 persons. About one-half had mild or moderate clinical symptoms, but in 15 a severe attack developed (4 deaths), mostly among kitchen personnel who had consumed fairly large quantities of the infested sausage; in 14 persons (among those who showed no clinical symptoms together with one case of latent infection) the presence of (gastric) anacidity (4 cases) and hypoacidity (7 cases) was revealed by the alcohol test meal. Further *in vitro* tests were undertaken to ascertain in which portion of the alimentary tract liberation of the encapsulated parasites occurs. Samples of the infected minced pork were subjected, for 2 hours at 37° C., to the action of 1% pepsin, normal human gastric juice, anacid human gastric juice, and for 3 to 24 hours to the action of five samples of heterogeneous origin of alkaline duodenal juice. The extent of liberation of the encapsulated parasites was proportional to the degree of acidity of gastric juice, being highest (100%) when acidity was 41 to 63%; in most tests (2 out of 3) the anacid juice did not dissolve the capsule, and only 2·9 to 17·9% of parasites were freed from their capsules after 3 to 24 hours' exposure to duodenal juice. It is concluded that in individuals with normal gastric secretion trichiniasis is apt to be severe while in those with anacidity or hypoacidity infestation tends to be mild or latent. *H. P. Fox*

OTHER INFECTIOUS DISEASES

2643. **Reiter's Disease: A Study of 344 Cases Observed in Finland.** [In English]
I. PARONEN. *Acta Medica Scandinavica* [*Acta med. scand.*] Suppl. 212, 1–112, 1948. 2 figs., bibliography.

Many cases of Reiter's disease were observed after an epidemic of dysentery in 1944 on the Karelian isthmus in Finland. The described series covers 344 such patients but the records of 10 have been lost; 310 were men and 34 women, while 288 were between the ages of 21 and 40 (extremes 2 and 55). In 97% joints were involved and in 89·2% the eyes, while 79·3% had abnormalities of the urogenital system. In 69·1% the onset was monosymptomatic, involvement of the eyes and urogenital system being the common combination, while in only 8% did the entire triad appear at once. All three of the cardinal signs were finally evident in 69·8%; in 71·4% of those showing all three the lesions appeared within the first 10 days though occasionally a symptom was delayed for as long as 100 days after the onset.

Arthritis, present in 325 cases, involved more than one joint in 316. In 82·5% articular swelling was noted but in 17·5% only arthralgic pains were present. The most commonly involved joints were knee, ankle, toes, shoulder, wrist, fingers, metatarsals, sacro-iliac, elbow, vertebrae, and hip, in that order. Exudate from the knee-joint was examined in 30 cases. It was greenish-yellow and viscous, and usually contained up to 90% neutrophil granulocytes, but sometimes lymphocytes predominated. Radiological examinations were made of 76 joints but in none were the findings abnormal.

Ocular involvement was noted in 298 patients—acute conjunctivitis in 239, kerato-conjunctivitis in 13, iritis in 11, corneal ulcer in 4, and iridocyclitis in 8; 20 others had mild ocular symptoms without any obvious lesions. In 80% of those with conjunctivitis both eyes were simultaneously involved. Smears and cultures of the ocular discharges were negative.

Nine patients had albuminuria; 29 out of 30 specimens of urine gave negative results on culture but *Salmonella paratyphi* B was found in 1 case. Although 103 had urethritis alone, in 63 others the urethritis was combined with a macular eczema of the penis, in 11 with a suppuration or ulceration of the penis, in 24 with a reddening of the meatal margin, in 12 with dysuria, in 4 with haematuria, in 9 with nephropathy, and in 9 with involvement of the testis or epididymis. Ten others had a macular eczema of the penis, 14 dysuria, and 3 pain in the testes or penis without obvious urethritis. No bacteria were generally found in the urethral discharge which, in about half the cases, cleared up in the first week and in 87% by the fourth week. Twenty-two patients developed cystitis but cystoscopy revealed nothing abnormal. Penile skin lesions were observed in 87%.

A mild dry pleurisy was definitely diagnosed in 26 patients and was considered probable in 48 others; 23 patients had myocarditis and pericarditis, 16 myocarditis alone, and 3 pericarditis alone. The electrocardiogram was abnormal in 2. The carditis lasted for up to 5½ months and might occur as early as the first week of the disease, though in one case it was delayed until the thirty-second month. Hyperkeratotic skin lesions resembling rupia were only observed in 2 patients though erythematous intra-oral patches were seen in 9. One man developed a bilateral mastitis. On the basis of the axillary temperature 81·3% were considered febrile; of these 77% had become afebrile by the third week. Only 26 out of 319 patients had a normal erythrocyte sedimentation rate; readings were highest when articular symptoms were present. Anaemia (116 cases) was usually normochromic; in 48 patients the white cell count was above 10,000 per c.mm. and in 18 under 4,000.

In 53% articular swelling disappeared in 2 to 4 months. Those with only arthralgic pain generally recovered much more rapidly. Ocular symptoms disappeared in 2 days to 7 months, while 87% of urogenital symptoms had disappeared by the fourth week, though the urethritis persisted in rare cases for as long as 9 months. In 40 there was recurrence of eye lesions, in 6 of urogenital manifestations, and in 10 of arthritis.

Treatment generally consisted of amidopyrine or salicylates. Sulphonamides were of no value in 7 cases; 3 of 9 patients given gold salts said that they felt better. Of 120 given fever therapy two-thirds had symptomatic improvement, though the duration of the disease appeared

unaffected. There were no fatalities due to Reiter's disease in the entire series. Of the 344 patients 322 had recently had Flexner dysentery and only 12 contracted Reiter's disease without previous diarrhoea. It is calculated that dysentery affected about 150,000 individuals, of whom paradoxically only about 0·2% contracted Reiter's disease. In two-thirds of the cases the syndrome commenced 11 to 30 days after the onset of the dysentery. Out of 132 sera examined 61 gave a positive agglutination reaction to Flexner A+D+WX and 8 out of 24 positive results were obtained with joint fluid. Only 3 patients had positive serum reactions for syphilis. No spirochaetes were found in blood, urine, joint fluid, and urethral and conjunctival discharges.

[On the basis of this material Reiter's disease would appear to be definitely associated with dysentery though this relation has not been clearly substantiated elsewhere. The low incidence of extragenital keratosis blennorrhagica is striking. The collection of the immense amount of data presented in this work, which also includes an extensive bibliography of 150 (mainly Continental) references, is a very creditable achievement.]

R. R. Willcox

2644. **Hepatic Dysfunction in Infectious Mononucleosis; with Review of the Literature**

T. E. PETERSON. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 1258–1270, Oct., 1948. 1 fig., bibliography.

The author has examined 40 consecutive cases of infectious mononucleosis admitted to the University of Minnesota Hospital during a period of 15 months. In 21 there was definite evidence of hepatic dysfunction as shown by 3 or more of the 12 liver function tests employed, although only one patient had clinical evidence of jaundice and 4 patients had an enlarged liver (in 3 the swelling was tender). There were indications of hepatocellular and cholangiolar damage but in all function returned to normal within a short period. Liver function tests will confirm the presence of a hepatitis during the progress of the disease, but are of little assistance in differential diagnosis. *E. T. Ruston*

2645. **A Preliminary Report on Rheumatic Fever in Virginia**

C. M. MCCUE and L. F. GALVIN. *Journal of Pediatrics* [*J. Pediat.*] **33**, 467–483, Oct., 1948. 10 figs., 21 refs.

The authors present a statistical analysis from Virginia of 225 cases of rheumatic fever which were followed up for at least three years or until death. The average duration of the disease to date was 5·95 years. There was a positive family history in 17·3%, and a history of preceding haemolytic streptococcal infection in 50%. The mean duration of the first attack, mainly calculated from Taran's criteria of activity, was 6·4 months, and of the second attack 8 months. Cardiac involvement occurred in 83% during the active phase. Residual cardiac damage was found in 49%, but the period of observation was short. During the period 7·1% of the patients died. Of the 225 patients, 89 had one attack, 78 had two attacks, 38 had three, 7 had four, 6 had five, 3 had six, and 1 had 7 attacks—a total relapse rate of 61%.

R. S. Illingworth

2646. **Immunologic and Biochemical Studies in Infants and Children, with Special Reference to Rheumatic Fever. IV. Occurrence of Agglutinins in Normal and Abnormal Conditions**

P. F. DEGARA. *Pediatrics* [*Pediatrics*] **2**, 410–414, Oct., 1948. 8 refs.

In order to test the hypothesis that an inadequate immune response may be an important factor in rheumatic fever, the author studied the degree of production of agglutinins for *Streptococcus haemolyticus* in both normal and rheumatic individuals.

A total of 497 sera from 372 children was examined for agglutinins against three different strains of *Strep. haemolyticus*, β group A, agglutination in serum dilutions of 1 to 160 or more being designated as positive. The following groups of children were studied: (A) Children who had not been ill for at least one month preceding the test, including normal and rheumatic subjects. (B) Non-rheumatic children ill at the time of the test or during the preceding month. (C) Rheumatic children who had an intercurrent illness at the time of the test or during the preceding month. (D) Children with active rheumatic fever, with and without antecedent streptococcal infections.

The essential findings were: (1) Streptococcal agglutinins were found in 8·7% of group (A), with no difference in incidence between normal and rheumatic subjects. (2) After infections, presumably streptococcal in origin, approximately 46% of the children examined had high agglutinin titres for *Strep. haemolyticus*. There was no essential difference in the titres between rheumatic and non-rheumatic children. (3) Agglutinins for *Strep. haemolyticus* were present approximately to the same degree in children with active rheumatic fever but without antecedent infection as in normal children. (4) In active rheumatic fever, agglutinins were present in high titre in 82% of the patients with antecedent streptococcal infections. The author concludes that no evidence was obtained to indicate that the immune response of "susceptible" and rheumatic children to infections, presumably streptococcal in origin, is different from that of non-rheumatic subjects. *P. T. Bray*

2647. **Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever. II. Complement Titers in Normal Conditions**

P. F. DEGARA and H. P. GOLDBERG. *Pediatrics* [*Pediatrics*] **2**, 242–247, Sept., 1948. 1 fig., 24 refs.

The authors examined 107 normal healthy children for complement titre, using the 50% haemolysis method. Of the 128 serum samples examined, 83% lay between 0·0040 ml. and 0·0069 ml. complement titre; 6·3% had higher and 10·2% lower values. The values obtained did not vary with age, sex, or season of the year, nor did repeated samples from the same subject show any significant variation. *C. L. Oakley*

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ASSISTED BY

S. S. B. GILDER, B.Sc., M.B., B.S.

This journal is planned to provide the reader with a selection of abstracts of the more important articles appearing in medical periodicals published in different parts of the world. Comment by the abstracter, when thought necessary, is inserted between square brackets, usually at the end of an abstract. In some instances only the titles of articles are provided.

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